**Abílio Óscar Silva Reis**

# Contributes for Pulmonary Hypertension: From healthcare organization to a comprehensive patient clinical management

# Contributos para a Hipertensão Pulmonar: Da organização dos cuidados de saúde à gestão clínica global do doente

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Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Ciências e Tecnologias da Saúde, realizada sob a orientação científica do Professor Doutor Luís Almeida, Professor Afiliado da Faculdade de Medicina da Universidade do Porto e do Professor Doutor Gérald Simonneau, Professor Jubilado da Université Paris-Sud, France.

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**keywords**

Pulmonary hypertension, Pulmonary arterial hypertension, Healthcare organization, Pulmonary hypertension information technologies, Quality of Life, Health-related Quality of Life, and Disability

**abstract**

As a background for this Thesis, the author presents the definition and implementation of a healthcare organization system for Pulmonary Hypertension (PH) in Portugal and the development of a dedicated information technology system for PH management and clinical research (PAHTool™), in both cases he was actively involved.

Taking advantage of the clinical research potentialities created by the referral centers' network that was implemented and the availability of PAHTool™, the author and his colleagues conducted a series of studies to characterize the Portuguese PH population in terms of epidemiology, clinical characteristics, treatment options, outcomes, and Quality of Life and Disability impairment. All these studies have been published or accepted for publication by peer-reviewed scientific journals.

*"Pulmonary Hypertension in Portugal: 1st Data from a Nationwide Registry"* was a prospective, observational, multicenter registry from five PH centers in Portugal. Predominance of females (65.2%), relatively young patients (43.4±16.4 years) and idiopathic pulmonary arterial hypertension (IPAH) etiology (37.0%) were the most relevant findings in the pulmonary arterial hypertension (PAH) group. Most patients were treated with single (50%), double (28%) or triple (9%) combination therapy. The 1-year survival estimate was 93.5% and 93.9% for the PAH and chronic thromboembolic pulmonary hypertension (CTEPH) groups, respectively. The main findings of this registry were in line with that of other international registries.

*"Pulmonary Hypertension: Real-world Data from a Portuguese Expert Referral Center"* was a retrospective analysis of a cohort of 101 patients with pre-capillary PH (pcPH) referenced to an expert tertiary care referral center in northern Portugal, from 2002 to 2013. This study provided long-term (3.8±2.7 years) real-world data of a predominantly incident population (80.2%), where the most relevant demographic findings were the female gender predominance (66.3%) and the relatively young age of the population (49.6±19.6 years). The high number (>60%) of patients in advanced stage of the disease at presentation suggested delayed diagnosis and highlighted the need to increase PH awareness among clinicians and explains why most patients were treated with combination therapy (53.2%). There was a significant improvement of World Health Organization functional class (WHO FC) ($p<0.003$), 6-minutes walking distance (6MWD) ($p=0.003$), mean pulmonary artery pressure (mPAP) ($p=0.002$), and pulmonary vascular resistance (PVR) ($p=0.008$), without significant changes in mean right atrial pressure (mRAP) and cardiac index (CI). The cumulative probability of survival at

1-, 3- and 5-years for the total cohort (respectively 86.6%, 76.7%, 64.1%), PAH (91.8%, 80.3%, 66.2%) and CTEPH (81.5%, 75.3%, 67.3%) and the substantial proportion of patients with idiopathic/heritable pulmonary arterial hypertension (I/HPAH) treated with triple combination therapy (61.1%) highlight the access to modern targeted therapies and compliance with international guidelines.

*"Long-term Survival in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: Insights from a Referral Center in Portugal"* intended to assess the long-term survival of a cohort of 142 patients followed up in a Portuguese referral center. This study showed that comparing the cohorts of patients treated in two periods, 2011-2016 and 2005-2010, a trend toward improved survival at 5 years was found for connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) (67% vs 33%) and CTEPH (84% vs 77%), but not for patients with I/HPAH (75% vs 84%). Earlier diagnosis, increasing use of parenteral prostanoids, and improvement of surgical treatments (pulmonary endarterectomy and lung transplantation) access were deemed necessary to further improve PAH and CTEPH patient's outcomes.

*"Portuguese Validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Questionnaire"* was a study aiming to translate and validate the CAMPHOR questionnaire for the European Portuguese-speaking population. Good internal consistency and reproducibility, as well as excellent convergent reliability and group validity was found for the Portuguese version of the CAMPHOR questionnaire.

In *"Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study"* it was demonstrated that HRQoL, measured by two different patient-reported outcomes measures (PROMs) (CAMPHOR, a PH-specific questionnaire, and Nottingham Health Profile, a general one), is impaired in Portuguese patients with PAH and other forms of pcPH, particularly in patients with increased disease severity. WHO FC, 6MWD, and Borg dyspnea index were highly correlated with health-related quality of life (HRQoL), measured by both instruments and quality of life (QoL), measured by CAMPHOR.

In *"Disability and Its Clinical Correlates in Pulmonary Hypertension Measured Through the World Health Organization Disability Assessment Schedule II (WHODAS 2.0): a prospective, observational study"* the studied PH population showed mild disability, with higher degree of disability in the domains of Mobility and Life activities. WHODAS 2.0 scores at baseline were robustly predictive of 6MWD and WHO functional class evolution. This study was the first one to assess disability in PH patients, using WHODAS 2.0.

**palavras-chave** Hipertensão pulmonar, Hipertensão arterial pulmonar, Organização de cuidados de saúde, Tecnologias de informação na hipertensão pulmonar, Qualidade de Vida, Qualidade de Vida Relacionada com a Saúde e Incapacidade funcional

**resumo**

Como enquadramento desta Tese, o autor apresenta a definição e implementação de um sistema de organização de cuidados de saúde para a hipertensão pulmonar (HP) em Portugal e o desenvolvimento de um sistema de informação dedicado para a gestão e investigação clínica da hipertensão pulmonar (PAHTool™), em ambos os projetos o autor teve participação ativa.

Aproveitando as potencialidades de investigação clínica criadas pela rede de centros de referência implementada e pela disponibilidade do PAHTool™, o autor e os seus colegas realizaram uma série de estudos para caracterizar a população de doentes com HP em Portugal, em termos de epidemiologia, características clínicas, opções de tratamento, resultados clínicos e repercussões na qualidade de vida e capacidade funcional. Todos os estudos realizados foram publicados ou aceites para publicação em revistas científicas com revisão por pares.

*"Hipertensão Pulmonar em Portugal: 1$^{os}$ Dados de um Registo Nacional"*, foi um registo prospetivo, observacional e multicêntrico, de cinco centros em Portugal. A predominância do género feminino (65.2%), de doentes relativamente jovens (43.4±16.4 anos) e da etiologia hipertensão arterial pulmonar idiopática (37,0%) foram os resultados mais relevantes do grupo com hipertensão arterial pulmonar. A maioria dos doentes foi tratada com um fármaco vasodilatador pulmonar específico (50%); 28% dos doentes foram tratados com combinação de dois destes fármacos e 9% com a combinação de três. A estimativa de sobrevivência a 1 ano foi de 93,5% e 93.9% para os grupos hipertensão arterial pulmonar e hipertensão pulmonar tromboembólica crónica, respetivamente. Os resultados principais deste primeiro registo português foram semelhantes aos de outros registos internacionais.

No estudo *"Hipertensão Pulmonar: Dados do Mundo Real de um Centro Especializado de Referência Português"*, fez-se uma análise retrospetiva de 101 doentes com HP pré-capilar, referenciados para um centro de referência de cuidados terciários no norte de Portugal, durante os anos de 2002 a 2013. Este estudo forneceu dados de vida-real a longo prazo (3,8±2,7 anos), de uma população predominantemente incidente (80,2%), onde os resultados demográficos mais relevantes foram a predominância do género feminino (66,3%) e de doentes relativamente jovens (49,6±19,6 anos). A apresentação da maioria dos doentes (>60%) em risco intermédio ou alto de mortalidade sugere um atraso no diagnóstico da doença e aconselha a uma maior divulgação desta entidade entre os profissionais de saúde e explica a utilização de tratamento combinado com várias drogas na maioria da população (53,2%).

Houve uma melhoria significativa da classe funcional da Organização Mundial de Saúde (p<0,003), da distância percorrida no teste dos 6 minutos de marcha (p=0,003), da pressão média da artéria pulmonar (p=0,002) e da resistência vascular pulmonar (p=0,008), sem alterações significativas do valor da pressão média da aurícula direita e do índice cardíaco. A probabilidade cumulativa de sobrevivência aos 1, 3 e 5 anos foi de respetivamente 86,6%, 76,7% e 64,1% para a coorte total, 91,8%, 80,3% e 66,2% para o grupo hipertensão arterial pulmonar, e 81,5%, 75,3% e 67,3% para o grupo hipertensão pulmonar tromboembólica crónica. A elevada percentagem de doentes com hipertensão arterial pulmonar idiopática/hereditária tratados com terapêutica combinada tripla (61,1%) reflete a facilidade de acesso às novas terapêuticas e o cumprimento das normas de tratamento aconselhadas pelas recomendações internacionais.

O estudo *"Sobrevivência a Longo Prazo na Hipertensão Arterial Pulmonar e na Hipertensão Pulmonar Tromboembólica Crónica: Dados de um Centro de Referência em Portugal"* pretendeu avaliar a sobrevivência a longo prazo de uma coorte de 142 doentes seguidos num centro de referência português. Comparando os doentes tratados no período de 2011-2016 versus o período de 2005-2010, verificou-se uma melhoria da sobrevivência a 5 anos para os doentes com hipertensão arterial pulmonar associada a doença do tecido conjuntivo (67% vs 33%) e da hipertensão pulmonar tromboembólica crónica (84% vs 77%), mas não para os doentes com hipertensão arterial pulmonar idiopática ou hereditária (75% vs 84%). O diagnóstico precoce, o aumento do uso de prostanóides por via parentérica e a melhoria do acesso aos tratamentos cirúrgicos da hipertensão pulmonar (endarterectomia pulmonar e transplante pulmonar) foram considerados necessários para atingir melhorias adicionais no prognóstico dos doentes com hipertensão arterial pulmonar e hipertensão pulmonar tromboembólica crónica.

O artigo *"Tradução e Validação para Português do Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR)"* descreve o processo de tradução e validação do questionário CAMPHOR para a população portuguesa com hipertensão pulmonar. Este estudo demonstrou a boa consistência interna e reprodutibilidade, bem como a excelente fiabilidade convergente e a validade de grupo da versão portuguesa deste questionário.

Em *"Qualidade de Vida Relacionada com a Saúde na Hipertensão Pulmonar e as suas Correlações Clínicas: Estudo Transversal"* demonstrou-se que a qualidade de vida relacionada com a saúde (HRQoL), medida por dois instrumentos (o CAMPHOR, um questionário específico para a hipertensão pulmonar e o Nottingham Health Profile, um questionário generalista), está comprometida na população portuguesa com hipertensão arterial pulmonar e outras formas de hipertensão pulmonar pré-capilar, particularmente nos doentes mais graves. A classe funcional da WHO, a distância percorrida no teste dos 6 minutos de marcha, a dispneia e o índice de Borg estiveram altamente correlacionados com o resultado da avaliação da HRQoL, medida por ambos os instrumentos e com a da qualidade de vida (QoL), avaliada pelo CAMPHOR.

Em *"Incapacidade e as suas Correlações Clínicas na Hipertensão Pulmonar Medida Através do World Health Organization Disability Assessment Schedule II (WHODAS 2.0): um Estudo Observacional, Prospetivo"* verificou-se que a população estudada apresentava incapacidade ligeira, com maior grau de incapacidade

nos domínios da Mobilidade e Atividades da vida diária. A pontuação do WHODAS 2.0 no início do estudo foi um preditor forte da evolução da classe funcional da WHO e da distância percorrida no teste dos 6 minutos de marcha. Este trabalho constituiu a primeira publicação da aplicação do questionário WHODAS 2.0 a doentes com hipertensão pulmonar.

## List of Abbreviations

| | |
|---|---|
| 6MWD: | 6-minutes walking distance |
| BPA: | Balloon pulmonary angioplasty |
| BMPR2: | Bone morphogenetic protein receptor type 2 |
| CAMPHOR: | Cambridge Pulmonary Hypertension Outcome Review |
| CHD-PAH: | Congenital heart disease-associated pulmonary arterial hypertension |
| CHP: | Centro Hospitalar do Porto |
| CI: | Cardiac index |
| CO: | Cardiac output |
| CTD-PAH: | Connective tissue disease-associated pulmonary arterial hypertension |
| CTEPH: | Chronic thromboembolic pulmonary hypertension |
| DGS: | General-Directorate of Health |
| DPG: | Diastolic pressure gradient |
| eCRF: | Electronic case report form |
| EHR: | Electronic health record |
| EIF2AK4: | Eukaryotic translation initiation factor 2 alpha kinase 4 |
| EMA: | European Medicines Agency |
| ERA: | Endothelin receptor antagonists |
| EU: | European Union |
| ERN: | European Reference Network |
| FC: | Functional class |
| FDA: | US Food and Drug Administration |
| HCP: | Healthcare provider |
| HIV: | Human immunodeficiency virus |
| HP: | Hipertensão pulmonar |
| HRQoL: | Health-related quality of life |
| ICD: | International Classification of Diseases |
| ICF: | International Classification of Functioning, Disability and Health |
| IPAH: | Idiopathic pulmonary arterial hypertension |
| I/HPAH: | Idiopathic/Heritable pulmonary arterial hypertension |
| MeDRA: | Medical Dictionary for Regulatory Activities |
| mPAP: | Mean pulmonary arterial hypertension |
| mRAP: | Mean right atrial pressure |
| NHP: | Nottingham Health Profile |
| OMIM: | Online Mendelian Inheritance in Man |
| ORDO: | Orphanet Rare Disease Ontology |
| PAH: | Pulmonary arterial hypertension |
| PAH-SYMPACT: | Pulmonary Arterial Hypertension-Symptoms and Impact |
| PAWP: | Pulmonary arterial wedge pressure |
| PcPH: | Pre-capillary pulmonary hypertension |
| PDE5i: | Phosphodiesterase type 5 inhibitors |
| PEA: | Pulmonary endarterectomy |
| PFDD: | Patient-focused drug development |
| PH: | Pulmonary hypertension |
| PRO: | Patient-reported outcomes |
| PROM: | Patient-reported outcomes measures |
| PVR: | Pulmonary vascular resistance |
| QoL: | Quality of Life |
| RHC: | Right heart catheterization |

| | |
|---|---|
| sGC: | Guanylate cyclase stimulators |
| UDVP: | Unidade de Doença Vascular Pulmonar |
| VTE: | Venous thromboembolism |
| UMLS: | Unified Medical Language System |
| WHO: | World Health Organization |
| WHODAS: | WHO Disability Assessment Schedule |
| WU: | Wood unit |

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# 1. CHAPTER I – Introduction and Thesis Structure

## 1.1. Introduction

### 1.1.1. Pulmonary Hypertension

Since the autopsy observation of the first case of "pulmonary vascular sclerosis" by Romberg in 1891,[1] a lot of "small steps" were taken to reach our current knowledge about pulmonary hypertension (PH).

One of the most important steps, very well emphasized by Alfred Fishman,[2] was the introduction of right heart catheterization (RHC), between 1940–50, leading this author to consider two distinct "eras" in PH research: before and after the introduction of hemodynamic studies. This pioneering statement is still valid nowadays, as RHC remains the gold standard for PH definition, classification and follow-up assessment.[3–5]

Another important step was the launch of periodic World Symposia on PH supported by the World Health Organization (WHO), in 1973, following the epidemy of pulmonary hypertension (PH) in Austria, Germany, and Switzerland caused by aminorex, an appetite suppressant drug, in the sixties and seventies of the XX$^{th}$ Century.[6] A clinical classification of PH, based in five groups, was proposed for the first time to the second WHO symposium on PH, in 1998.[7] Since then, these meetings were both the place for analysis and discussion of evidence published in between them (after meticulous work and discussion between the members of the different working groups) and the source of guidelines and recommendations for the following years.[8–10] The most recent PH World Symposium took place in 2018, in Nice, France, and the PH community is waiting for the publication of the respective proceedings and updated guidelines.

In the last fifty years, the intense basic research on PH lead to a better understanding of its pathobiology and genetics. At the same time, continued epidemiological and clinical research, as well as the discovery of new drugs and different strategies to use them, brought great improvements in the clinical management of PAH patients.[11–15] Such improvements lead, ultimately, to a complete transformation in the various facets of patients' lives, including functionality, prognosis, survival, and quality of life (QoL).[16,17] However, despite these tremendous progresses PAH patients prognosis maintains unacceptable bad and we are yet far from getting a cure for this devastating group of diseases.[18]

Today, as can be seen in table 1, we know that PH is a common complication of frequent diseases such as left heart (group 2) and lung diseases (group 3)—the most frequent forms of PH—or it can present as an isolated form with a genetic background component (heritable) or not (most forms of idiopathic); it can also be induced by some drugs (e.g. aminorex, fenfluramine derivatives, benfluorex, and selective serotonin reuptake inhibitors) and toxins or associated with other diseases or risk factors (connective tissue disorders, HIV infection, liver diseases with portal hypertension and congenital heart diseases). These last forms are designated as Pulmonary Arterial Hypertension (PAH or group 1) and together with Chronic Thromboembolic Pulmonary Hypertension (CTEPH or group 4) are the "core" of attention of the scientific community and the only forms of PH with indication for treatment with specific pulmonary vasodilators drugs.[8,10] CTEPH is a particular form of PH linked to acute or chronic venous thromboembolism (VTE) and demands careful and specific clinical management since it is a potentially curable disease.[19] Some other diseases can be accompanied of PH by unclear and/or multifactorial mechanisms (group 5).

The last update of the clinical and hemodynamic PH classification was proposed in the World Symposium of Nice, in 2015 (Tables 1 and 2) and integrates the current guidelines for PH diagnosis and treatment.[8,10]

**Table 1. Clinical classification of pulmonary hypertension, as updated from Simonneau et al.**[20]

| **1. Pulmonary arterial hypertension** | **2. Pulmonary hypertension due to left heart disease** | **4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions** |
|---|---|---|
| 1.1 Idiopathic<br>1.2 Heritable<br>1.2.1 BMPR2 mutation<br>1.2.2 Other mutations<br>1.3 Drugs and toxins induced<br>1.4 Associated with:<br>1.4.1 Connective tissue disease<br>1.4.2 Human immunodeficiency virus (HIV) infection<br>1.4.3 Portal hypertension<br>1.4.4 Congenital heart disease<br>1.4.5 Schistosomiasis | 2.1 Left ventricular systolic dysfunction<br>2.2 Left ventricular diastolic dysfunction<br>2.3 Valvular disease<br>2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies<br>2.5 Congenital/acquired pulmonary veins stenosis | 4.1 Chronic thromboembolic pulmonary hypertension<br>4.2 Other pulmonary artery obstructions<br>4.2.1 Angiosarcoma<br>4.2.2 Other intravascular tumors<br>4.2.3 Arteritis<br>4.2.4 Congenital pulmonary arteries stenosis<br>4.2.5 Parasites (hydatidosis) |
| **1'. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis**<br>1'.1 Idiopathic<br>1'.2 Heritable<br>1'.2.1 EIF2AK4 mutation<br>1'.2.2 Other mutations<br>1'.3 Drugs, toxins and radiation induced<br>1'.4 Associated with:<br>1'.4.1 Connective tissue disease<br>1'.4.2 HIV infection | **3. Pulmonary hypertension due to lung diseases and/or hypoxia**<br>3.1 Chronic obstructive pulmonary disease<br>3.2 Interstitial lung disease<br>3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern<br>3.4 Sleep-disordered breathing<br>3.5 Alveolar hypoventilation disorders<br>3.6 Chronic exposure to high altitude<br>3.7 Developmental lung diseases | **5. Pulmonary hypertension with unclear and/or multifactorial mechanisms**<br>5.1 Hematological disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy<br>5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis, neurofibromatosis<br>5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders<br>5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension |
| **1". Persistent pulmonary hypertension of the newborn** | | |

BMPR2 = bone morphogenetic protein receptor, type 2; EIF2AK4 = eukaryotic translation initiation factor 2 alpha kinase 4; HIV = human immunodeficiency virus. Adapted from Galiè et al. Eur Respir J. 2015;46(4):903-975.

**Table 2. Hemodynamic definitions of pulmonary hypertension.**

| Definition | Characteristics | Clinical group(s) |
|---|---|---|
| PH | PAPm ≥25 mmHg | All |
| Pre-capillary PH | PAPm ≥25 mmHg<br>PAWP ≤15 mmHg | 1. Pulmonary arterial hypertension<br>3. PH due to lung diseases<br>4. Chronic thromboembolic PH<br>5. PH with unclear and/or multifactorial mechanisms |
| Post-capillary PH | PAPm ≥25 mmHg<br>PAWP >15 mmHg | 2. PH due to left heart disease<br>5. PH with unclear and/or multifactorial mechanisms |
| Isolated post-capillary PH (Ipc-PH) | DPG <7 mmHg and/or<br>PVR ≤3 WU | |
| Combined post-capillary and pre-capillary PH (Cpc-PH) | DPG ≥7 mmHg and/or<br>PVR >3 WU | |

CO: cardiac output; DPG: diastolic pressure gradient (diastolic PAP – mean PAWP); mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; WU: Wood units. Adapted from Galiè et al. Eur Respir J. 2015;46(4):903-975.

Classifying PH patients according to the PH clinical classification is of major importance to define a clinical management strategy, namely in terms of drug selection (Table 3). Only group 1 forms of PH (PAH) and some group 4 (CTEPH) patients have indication for treatment with specific pulmonary vasodilators and/or specific interventional or surgical treatments (pulmonary balloon angioplasty, pulmonary endarterectomy or lung transplantation).

**Table 3. Treatment approaches according to PH etiology.**

| PH etiology | Treatment |
|---|---|
| Group 1 | Endothelin receptor antagonists (ERA), phosphodiesterase type 5 inhibitors (PDE5i), guanylate cyclase stimulators (sGC), prostacyclin analogues and prostacyclin receptor agonists |
| Group 2 | Diuretics, beta-blockers, angiotensin-converting enzyme inhibitors (ACEi) |
| Group 3 | Oxygen, bronchodilators (BDL), noninvasive ventilation (NIV) |
| Group 4 | Pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), riociguat |
| Group 5 | Unknown |

Group 1 and group 4 forms of PH have a low incidence (2.4-7.6 and 5 cases per million, respectively) and prevalence (15-52 and 38.4 cases per million, respectively)[21,22] and are considered rare diseases, requiring a special healthcare organization, centered in dedicated referral centers.[8,10,23,24]

A precise etiologic diagnosis is crucial for the determination of patient prognosis and for establishing the best treatment approach. The diagnostic algorithm

recommended by the guidelines defines very well the steps and tools to get a precise etiology. A considerable number of invasive and non-invasive tests are recommended; their correct technical execution and clinical interpretation are determinant of the results. This is the reason why most of them should be done in specialized centers with a high volume of tests to provide the experience to get the best information from them. This complexity of the diagnostic work-up also requires specialized organization to get the best results. Multidisciplinary discussion between experienced experts in PH to integrate test results with the clinical picture should also be routinely done in the clinical management of PH.

Current treatment of PAH, mainly medical treatment with specific pulmonary vasodilator drugs, has improved patients prognosis and survival dramatically, from a median survival of 2.8 years[25] in the 1980s to around 9 years nowadays.[26] These results have evolved progressively during the past two decades thanks to a better understanding of PAH pathophysiology and identification of three main pathways implicated in the onset and progression of the disease—endothelin, nitric oxide, and prostacyclin pathways—thus representing meaningful targets for therapeutic interventions.[14] Numerous targeted PAH drugs were developed and approved (bosentan, ambrisentan, macitentan, sildenafil, tadalafil, riociguat, epoprostenol, iloprost, treprostinil, beraprost and selexipag) and used as monotherapy or in combination therapy.[27–30] Furthermore, a trend emerged in clinical trials design in PAH from short-term, scarce endpoints (e.g. WHO FC, 6MWD, hemodynamic parameters and others) evaluation towards long-term outcome studies using composite morbidity and mortality endpoints.[31,32]

Recent cohort studies and meta-analysis indicate that aggressive treatment strategies with early combination therapies are associated with improved outcomes.[27,28,33,34] These outcomes depend mainly on the definition of a correct treatment strategy that includes: (1) continuous patient risk of 1-year mortality assessment; (2) best use of drugs according to risk stratification (monotherapy or combination therapy, and this last one as sequential add-on or as upfront combination of drugs); and (3) pursuing objectives, trying to bring and keep the patient in the low risk of 1-year mortality zone .[35–39] PAH and CTEPH patient's clinical management in a referral center, and the availability and accessibility to medical and surgical treatments, are other important determinants of outcomes.[40,41]

### 1.1.2. Healthcare organization in Pulmonary Hypertension

The rare condition of PAH and CTEPH coupled with the complex work-up diagnostic approach and difficult treatment decisions, as well as the high costs associated with their clinical management [42,43] lead to a consensus among stakeholders towards the implementation of country or multinational networks based in referral centers.[23,24] Most European countries have their national networks for rare diseases and, recently, the European Reference Network (ERN) for rare and low prevalence complex diseases, including PH, was implemented by the European Commission.[44] Today it is unquestionable that national networks for rare diseases improve disease management, including disease awareness, early referral to expert centers, diagnosis, and facilitate access to recommended treatments. As a natural consequence, patients achieve better outcomes in terms of functionality, quality of life, and survival. Furthermore, this type of organization can provide data for healthcare planning and cost control.

Regional networks, such as ERN, allow for mutual consultancy between centers as well as cross-border care. This kind of organization provide the patients served by the network access to the most sophisticated care. The concentration of a high number of patients in referral centres also allows highly specialized centers to gain high-volume-based knowledge and experience in rare procedures (balloon septostomy, bronchopulmonary angioplasty, pulmonary endarterectomy and lung transplantation), which improves the quality of care and optimizes resources utilization with the respective cost savings.[45–48]

### 1.1.3. Information systems in Pulmonary Hypertension

A dedicated healthcare organization for rare diseases should be supported by specific electronic systems, which ideally should integrate and communicate with other electronic data-generating systems.[49] Modern information technologies provide the possibility to design dedicated software able to help and educate PH teams and to support investigators in their clinical and research activities. Real-world databases for research can be built while performing routine daily clinical activities. Flexible and dynamic systems, giving the possibility of personal customization, can be offered to users according to their needs and wishes. Common electronic Case Report Forms (eCRF) can be designed for clinical studies. Current cloud hosting technology makes it easy to build big data banks for research.[50]

Demographic, clinical and biobank data can be combined for research in the field and to advance towards personalized medicine.[51] Information retrieved from this type of electronic support can help in developing knowledge about PH epidemiology (i.e. registries), patient characterization (phenotypes and genotypes), and outcomes, as well as improving quality and financial management by healthcare providers and authorities. Real-world clinical studies based on structured data coming from daily practices are also of uppermost importance for the development and approval of innovative therapies.[52]

PH registries conducted to date were an important source of information and contributed for great advances in the knowledge of epidemiology, clinical characteristics, interventions and outcomes of this population. Still, some weaknesses and difficulties can be found[53]: most registries are not representative of real-world patient population because of selection bias; missing data is also a common issue and most of them are not true prospective studies; furthermore, the data collection methodology usually implies double record of patient data, which, in addition to the added work and resources consumption, further contributes to selection bias and missing data.

Therefore, improved dedicated electronic tools are needed. They should be specifically designed to be user friendly and actually help PH teams in their clinical and research activities; they should be flexible, dynamic and customizable, in order to generate eCRFs, with mandatory fields, in a way that provides structured data for automatic reports and data analysis. Additionally, the integration/communication with other electronic systems generating health data is of paramount importance for a better understanding of these groups of diseases and for the improvement of healthcare quality and outcomes, as well as planning and regulation.[54]

### 1.1.4. Quality of life and disability in Pulmonary Hypertension

According to the WHO's concept of health—"A state of complete physical, mental, and social well-being not merely the absence of disease"—, patient evaluation should be extended over the physical aspects (e.g. clinical measures, biomarkers and others) and include Quality of Life (QoL) and/or Health-related QoL evaluation (HRQoL).[55]

Defining the concepts of health status, HRQoL, and QoL is yet a matter of controversy among experts, which is well expressed in the medical literature.[56] Health status is defined as the narrower of the three concepts, including all aspects of physical, mental, and social functioning that characterize an individual at a given time. HRQoL, on the other hand, evaluates the effects of the physical, mental, and social aspects, and particularly the effects of illness and treatment, on the individual's sense of well-being. QoL is the broader of the three concepts covering all aspects of life, including non-health-related aspects such as economic status, social participation, and others, to characterize an individual's overall sense of well-being. Specifically, the WHO defines QoL as "an individual's perception of his position in life in the context of the culture and value systems in which he lives and in relation to his goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of his environment".[55]

Recommendations from the 4$^{th}$ and 5$^{th}$ World Symposium on PH reinforce the importance of measuring patient-reported outcomes (PRO) as a secondary end-point in clinical trials.[57,58] These developments reflect the rising importance attributed to the patient voice in the drug development and approval process across therapeutic areas.[59] Importantly, the US Food and Drug Administration (FDA) has implemented a Patient-Focused Drug Development (PFDD) initiative, intended to bring patient perspectives into the early stages of product development.[60] After conducting a public meeting to capture patients' perspectives about their disease and its impact on their daily life, the FDA has established guidance providing clear scientific standards for clinical outcome assessment in PAH,[61] defining a patient-reported outcome measure (PROM) as a report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else.[62]

Numerous PROMs for the assessment of QoL/HRQoL are available for the general population, but few have been validated for PH. Most of them are used in multiple diseases and are called general PROMs. CAMPHOR is the only PROM specifically created and validated to assess HRQoL and QoL in PH (i.e. PH-specific PROM). All these instruments are difficult to apply because of their extension, they have a large number of questions, which makes them very time-consuming and most of them require interpretation by a clinician. Thus, simpler and easier to use questionnaires, some of them already approved by regulatory agencies, such as emPHasis-10 [63,64] and Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®),[65,66] have been proposed and are under evaluation, including for use in clinical trials.[67]

The use of PROMs is a very important component in evaluating the global health state of patients and a fundamental piece towards patient-centered, patient-engaged, and self-managed medicine.

In addition to HRQoL/QoL evaluation, it is also very important in the management of PH patients to define and evaluate functionality/disability given the highly debilitating nature of these groups of diseases. The WHO also developed the International

Classification of Functioning, Disability and Health (ICF), which provides an integrative approach to evaluate the level of health and disability at both individual and population levels.[68] ICF is operationalized through the WHO Disability Assessment Schedule (WHODAS 2.0),[69] which is an instrument for assessing health status and disability across different populations and settings, while providing a more accurate basis for comparisons between diseases.

## 1.2. Thesis Structure

The proper management of a rare and highly debilitating disease such as Pulmonary Arterial Hypertension requires a centralized healthcare organization system, facilitated access to accurate and vast clinical and nonclinical patients' data on an electronic repository, and the availability of tools able to capture patient-reported outcomes and other forms of patient assessment. The work reported in this Thesis aimed to contribute to fill some of the gaps in PH management in Portugal.

This Thesis is organized in five chapters.

In Chapter I, the author describes pulmonary hypertension and the complexities associated to its management. Furthermore, areas requiring research and development are identified, constituting the scientific background for the research conducted by the author and his associates.

In Chapter II the author presents the organizational context in which his research has been developed, and for which he has played an active role, namely in the definition and implementation of the PH healthcare organization in Portugal and the development of a PH-specific information system (PAH Tool™) for use in PH management and clinical research.

Taking advantage of the favorable operational conditions characterized in Chapter II, the following investigational projects were planned and implemented, and their results are presented in Chapters III and IV, in the form of reprints from papers published by peer-reviewed scientific journals:

- To study the epidemiology, clinical characteristics and outcomes of Pulmonary Hypertension (PH) in Portugal (Chapter III), this chapter reports:
    - Data from a nationwide PH Registry.
    - Real-world data from a PH expert referral center.
    - Long-term survival data from a PH expert referral center.

- To study the QoL, HRQoL and Disability impairment in Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) populations (Chapter IV), this chapter reports:
    - Validation of a specific-PH QoL questionnaire (the CAMPHOR) for the Portuguese population.

- Results from the application of a PH-specific QoL questionnaire (CAMPHOR) and a general HRQoL questionnaire (NHP) to PAH and CTEPH populations.
- Disability assessment in PAH and CTEPH populations using the WHODAS 2.0 questionnaire.

In the last chapter (Chapter V), the author discusses what has been achieved and the prospects for future developments in PH management and draws his conclusions on the work done.

# 2. CHAPTER II – Pulmonary Hypertension healthcare organization

## 2.1. Centralized healthcare management system for Pulmonary Hypertension

PH encompasses a significant number of diseases, some of them rare, complex and life-threatening.[20] The low number of patients makes it difficult for them to have significant capacity for intervention with healthcare authorities and the society in general. As in most rare diseases, PAH and CTEPH require complex clinical management and treatment with high-cost drugs, that, if not adequately managed by the healthcare system, constitute a substantial financial burden for healthcare providers (e.g., hospitals), which can be a motive for resistance in accepting these patients. Taken together, all these facts lead to the recommendation for concentration of patients in highly specialized centers and the allocation of adequate financial resources.[23,24,43,70–72]

In the last 20 years, patients' and professionals' associations, healthcare providers organizations and pharmaceutical companies, have been working towards increasing awareness among healthcare authorities for the need of a dedicated healthcare organization with a dedicated budget in the field of PH.

The European Commission launched, in 2008, a special program to alert European countries for the need to find better healthcare organizations for the management of Rare Diseases.[71] These directives were followed by Council Recommendations that called on Member States to put national strategies in place[72] and for strengthening the balance in the pharmaceutical systems in the EU and its Member States.[70]

In Portugal, in 2008, during the national discussion process for the implementation of the directives from the European Commission for Rare Diseases, a project for PH healthcare organization was presented by the Study Group of Pulmonary Vascular Diseases of the Portuguese Internal Medicine Society and was accepted by the General-Directorate of Health (Direção Geral de Saúde, DGS). A Technical Commission, integrated in the Quality Department of DGS, was created to implement it.[73] The author of this thesis was nominated as coordinator of this Technical Commission.

The project (organization chart in Figure 1) was implemented: the 1st Portuguese Guidelines for PH were published,[74] applications for referral centers were opened,[75] and a dedicated information system was provided to the authorities to help on the regulation of clinical practices and costs.

Four referral centers fulfilled the required criteria and were nominated as official centers for the treatment of PH,[75] and a dedicated reimbursement budget was created for these centers. The Unidade de Doença Vascular Pulmonar do Centro Hospitalar do Porto, led by the author of this thesis, was one of the four appointed PH referral centers. A first national Registry was launched, to provide epidemiologic data to characterize the Portuguese PH population and served as a basis for healthcare planning.[76]

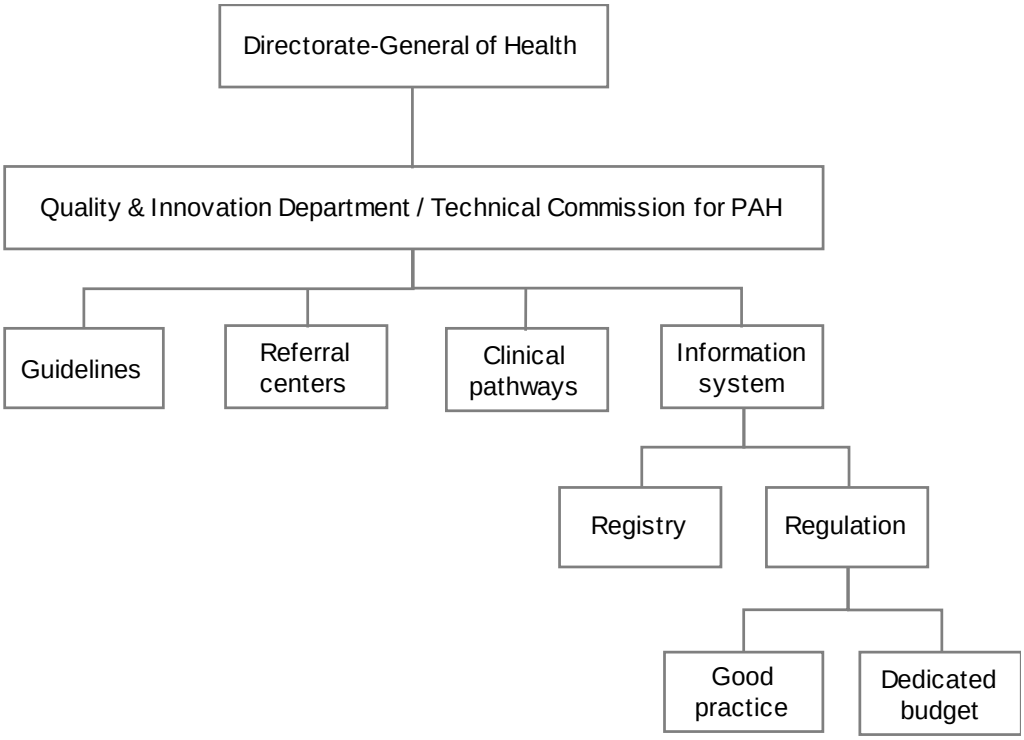



**Figure 1. PH Portuguese Organization Chart.**

The proposed organization was based on the experience from similar systems already implemented in other European countries, the best examples of which were the French and British systems.[24,77] The longstanding and tight relationship with the organizers of the French network was of foremost importance for the success of the initiative. Their continuous support, being present in numerous national and regional scientific meetings, where political discussion with authorities was fomented, was crucial to support the project. In addition, their support to meet care needs not existent in the Portuguese Network (Surgical treatment of PH: endarterectomy and lung transplantation), putting in place at the time a true cross-border healthcare, were and are invaluable contributes for the care of Portuguese PH patients.

## 2.2. Integration of the *Unidade de Doença Vascular Pulmonar do Centro Hospitalar do Porto* in the European Reference Network for rare and low prevalence complex diseases

The European Reference Networks (ERNs), created under the "Directive 2011/24/EU on patients' rights in cross-border healthcare"[78], were implemented to improve patient access to highly-specialized, high-quality, and safe care, pooling knowledge and improving diagnosis and care in medical fields where expertise is rare.

In 2017, the European Commission launched the ERN for rare and low prevalence complex diseases program. Twenty-four ERNs were created being the ERN-LUNG, dedicated to Rare Respiratory Diseases, one of them. The ERN-LUNG (https://ern-lung.eu) encompasses 9 groups of respiratory rare diseases, including the Pulmonary Hypertension group constituted by 17 Centers (illustrated in Figure 2). The sole Portuguese center belonging to ERN-LUNG is *Unidade de Doença Vascular Pulmonar*

*do Centro Hospitalar do Porto*, which is led by the author of this thesis, after a very demanding but successful application.

ERN-LUNG is defined as “a non-profit, international, professional, patient-centric and scientific network and it is committed Europe-wide and globally to the prevention, diagnosis and treatment of rare respiratory diseases through patient care and advocacy, education and research”. Integrating this network will surely have great benefits for Portuguese patients (access to all available therapies through cross-border care), professionals (consultancy, training and shared research projects), and healthcare providers (healthcare and organizational quality improvements as a result of benchmark and audits).

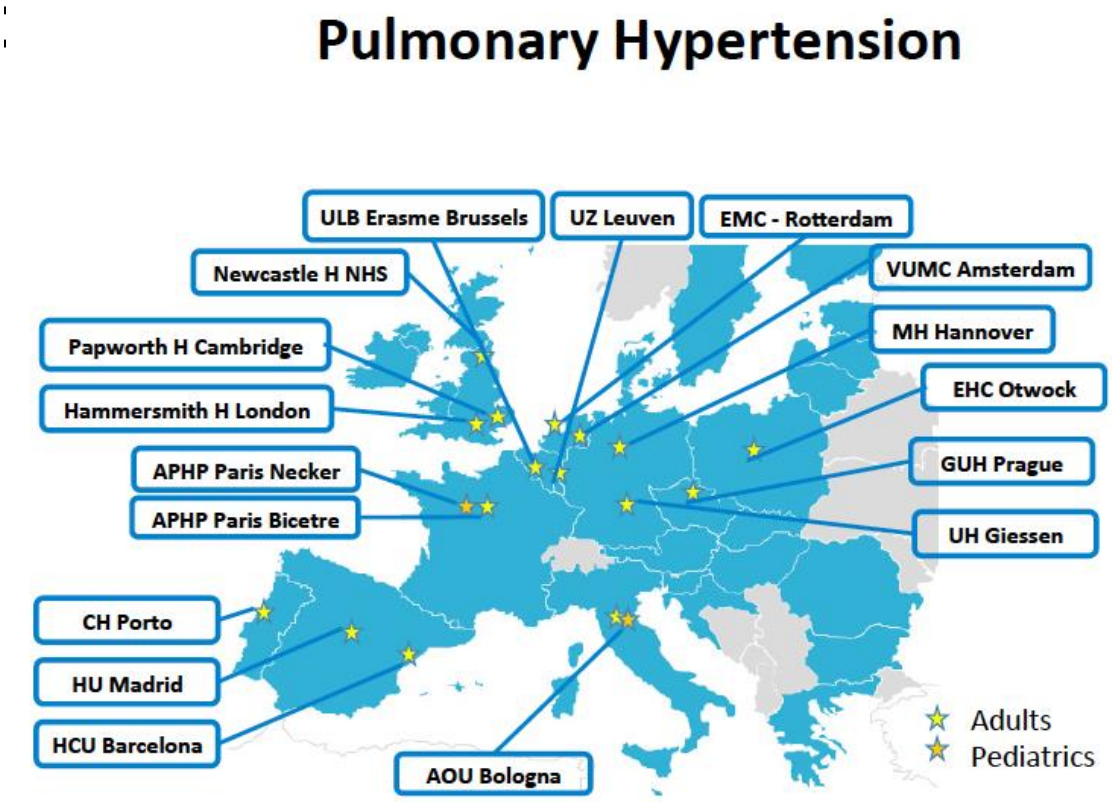



**Figure 2. PAH centers in the European Reference Network for rare and low prevalence complex diseases.** Source: https://ern-lung.eu, accessed on August 28th, 2018.

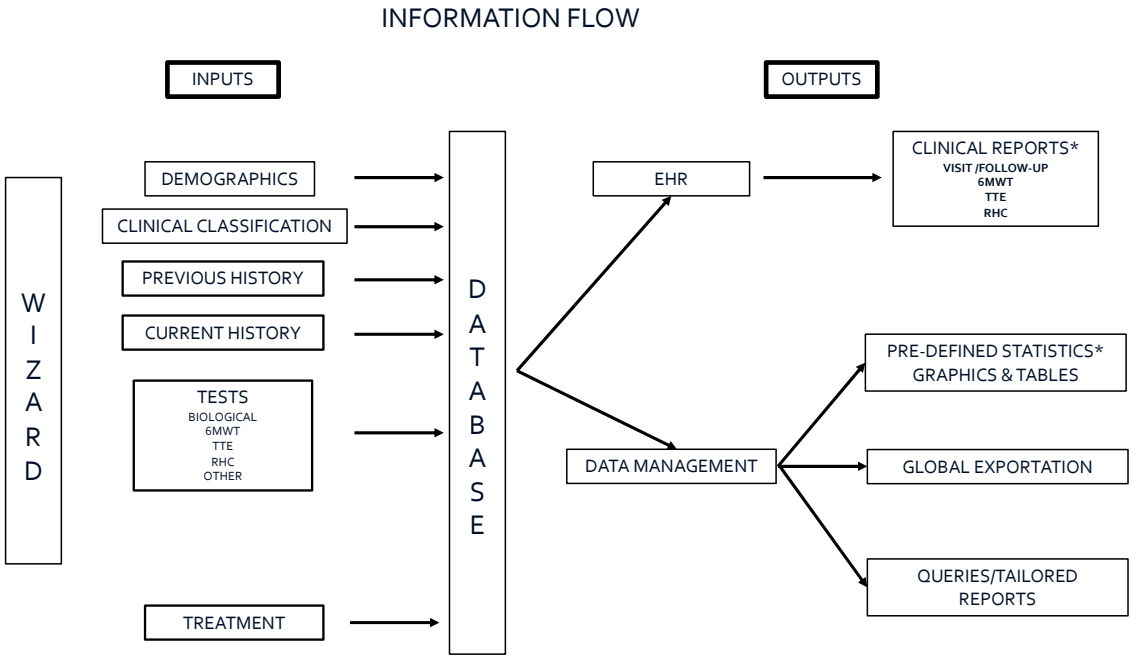
## 2.3. PAHTool™: An information technology tool for patient's management and clinical research in Pulmonary Hypertension

Modern information technologies have been revolutionizing access to information and the way we organize society.[79] Medicine, as a scientific discipline that is highly dependent on research and circulation of information, has benefited largely from the progresses in electronic access to information. Electronic technologies, with their great capacity of storage and high-speed access to data, provide new opportunities for the development of large and robust databases for clinical and investigational purposes. Modern computing technology allows the design of friendly and helpful systems to assist healthcare teams in their daily clinical practice. Telemetry and wearable technology allow the incorporation of in- or out-patient information introduced by the patient himself or collected from external portable devices (wearables).[67,80] Electronic Health Records (EHR) incorporating all these data can provide a huge amount of information, covering all aspects of the health state of the individual, and be a huge source of information for both healthcare and research. Cloud services give us the possibility to have universal systems and big data banks[81,82] at the distance of a click on the keyboard of a computer or a mobile device. Incorporation of artificial intelligence and machine learning in medical decision processes will assist the exercise of medicine in the future.[83–86] Such technological advances will allow the implementation of real-world clinical trials and registries in the near future.[87] Ultimately, advanced EHRs, which incorporate social/behavioral measures linked with biobanks and vital records collected from wearable devices, will greatly improve our understanding of disease, clinical care approaches, and overall public health.[80–82]

Due to its rare nature and complexity, PH requires highly specialized care in referral centers, which should be supported by dedicated information systems helping PH teams in their daily activities while storing real-world clinical information to provide databases for the evaluation of clinical activities, clinical research, and healthcare planning and regulation. To our knowledge, before the development of Pulmonary Arterial Hypertension tool (PAHTool™), there was no dedicated electronic information system for PH addressing all these objectives.

PAHTool™ (http://www.pahtool.net) was created by the author of this Thesis and a software company (Inovultus, Lda, Santa Maria da Feira, Portugal), in 2008. PAHTool™ is a software for PH disease management and clinical research and incorporates the most recent recommendations for clinical management of PH; these recommendations are organized in a wizard composed of specific pages (illustrated in Figure 3): identification, clinical classification, previous and current history, tests and treatments. This wizard is flexible and dynamic (fields can be visible or hidden, mandatory or not and new fields can be added) and customizable according to the user needs; a specific eCRF can be designed for each user project (center, national or international registry, clinical trial or other) and different eCRFs can coexist linked to the project name. "Clinical picture" (a summary of patient's demographic, clinical characteristics and treatments) and "Follow-up tables and graphics" (fast and easy way to evaluate patient evolution, including risk assessment, and make treatment decisions) are innovative implementations and extremely useful guides for fast and easy clinical decisions. Automatic generated tests and clinical reports are useful helpers for PH teams, saving their time and allowing them to send information to other information systems or to other healthcare providers. A section with patient "Synthesis" (discharge,

referral, lost to follow-up or death) provides information for clinical, administrative and outcomes analysis. All stored data are automatically exportable to an excel sheet or to other data analysis software, as a global export or in a "tailored" fashion (structured queries: user chooses filters and parameters to export). Pre-defined searches present automatically generated tables and graphics giving the user administrative (e.g. number of patients, visits, hospitalization types, others), demographic (age, gender), epidemiological (incidence, prevalence, time to diagnosis), clinical (presentation signs and symptoms, etiology, clinical evolution of main parameters, treatments), and outcomes (mortality and survival) information.




*automatic generated
6MWT: six-minutes walking test; TTE: transthoracic echocardiogram; RHC: right hear catheterization; EHR: electronic health record

**Figure 3. Information flow generated by PAHTool™.**

Integration of 2015 ESC/ERS guidelines clinical classification linked to the various nosology classifications (e.g. ICD, ORDO, OMIM, MeDRA, UMLS) make it possible to stratify patients in homogeneous sub-groups and to have robust information about true epidemiology, different demographic and phenotype/genotypic characteristics, as well as of outcomes according to different interventions. In addition, real-world structured information for research (e.g. clinical trials, registries, others) is permanently available without duplicating the user work.

PAHTool™ was tested in the UDVP of CHP, and later made available to other Portuguese centers and to the Portuguese authorities. It was hosted in a server of the General-Directorate of Health and made available as a cloud service to the official PH Portuguese centers. A national database was built powered by individual centers' data, which remained the "owners" of their data. Each center has an administrator that defines the user profile of their collaborators and participates in the decisions for studies sharing data. Some joint collaboration studies were produced and published[76] as well as single center studies, including all the papers of this thesis.[88–92]

In 2013, the French PH network leaders of the very well-known French national registry decided to move from their old tool to PAHTool™. A joint collaboration project was launched. PAHTool™ was reformulated according to the French network needs and migration of around 8,000 patients was done at the time. Since then PAHTool™ is the national platform for this very important PH registry and its database has been the source for the numerous publications of this highly active group.[93,94]
Other countries (13) and centers (69) adopted PAHTool™, which is now spread all over the World (Figure 4), serving at the moment 7 national Registries and including more than 20,000 PH patients.

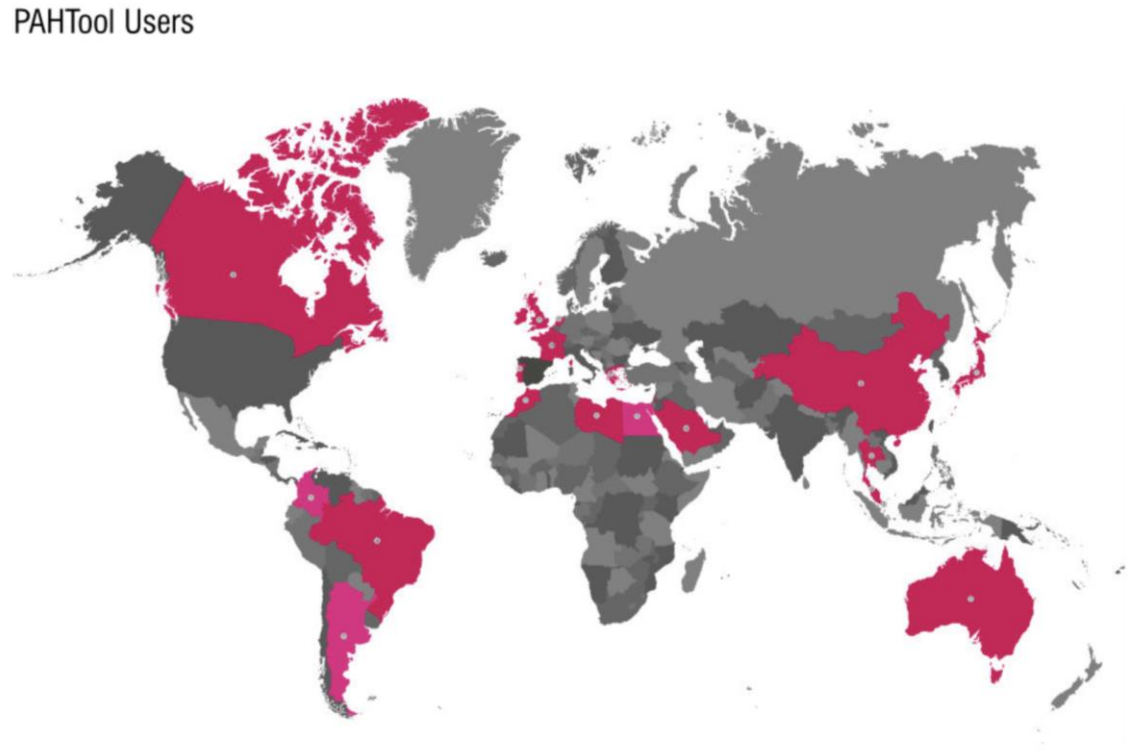



**Figure 4. Countries using PAHTool™.**
Source: http://www.pahtool.net/Customers.html, accessed on August 28th, 2018.

During the last 5 years numerous meetings were organized with PH experts and scientific PH organizations over the world, contributing to the improvement of the project and of the tool. An International registry of centers/countries using PAHTool™, with a common eCRF to answer specific questions: demographics, etiologies, patient phenotypes and presentation (risk assessment), prescribed drugs and treatment strategies as well as outcomes, is being discussed by the international group of PAHTool™ users.

**The organizational achievements presented above facilitated the implementation of the investigational projects that will be described in the next chapters**

# 3. CHAPTER III – Contributions to a better knowledge of PH national reality: epidemiology, clinical characteristics, and clinical outcomes

PAH is a rare condition that is not yet fully characterized. Over the years, several international registries and cohort studies contributed to establish the epidemiology and natural course of the disease in its various forms. But with the introduction of targeted disease-specific therapy it became increasingly important to assess patients' clinical characteristics and disease course in order to achieve the best possible patient outcomes and contribute to a better knowledge of epidemiology that could inform healthcare planning.

We conducted a prospective, observational, and multicenter registry with a joint collaboration from five centers around Portugal: *"Pulmonary Hypertension in Portugal: 1st Data from a Nationwide Registry",*[76] published in BioMed Research International (2013). This registry provided the first systematic data on the clinical characteristics and management of the PH population in Portugal. The overall incidence for PAH (1.5 to 2.2 patients per million) and CETPH (1.1 patients per million) was similar to that reported in other registries and cohort studies. Most (74.0%) patients were in WHO functional class III or IV, showing that they were diagnosed late in the course of their disease. CHD-PAH (21.7%) was found to be a frequent etiology which may warrant special attention to these diseases surgical repair during infancy. The one-year survival estimates for this incident cohort exceeded 93.0% for both PAH and CTEPH groups, a value that reflected access to contemporary medical treatment for PAH; in contrast, only 10.8% of CTEPH patients were submitted to pulmonary endarterectomy, and no patient was submitted to lung transplantation, which reflects difficulties of access to surgical treatments for PH patients in Portugal.

Later we conducted a long-term analysis (mean follow-up time of 3.8±2.7 years) of real-world data from a population of 101 patients with pre-capillary pulmonary hypertension, followed between 2002 and 2013 at a PH reference center in Porto, Portugal. *"Pulmonary Hypertension: Real-world Data From a Portuguese Expert Referral Centre",* [91] was published in Pulmonology (2018). The most frequent etiologies found were CHD (36.3%) followed by I/HPAH (32.7%) and CTEPH (25.7%). At presentation, patients showed mostly intermediate or high risk of 1-year estimated mortality (>60%), which could be indicative of delay in diagnosis and highlights the need to increase awareness among clinicians and promote early referral to expert centers. Most patients were treated with PAH-specific therapy (91.1%), as monotherapy (42.6%), double (29.7%) or triple (18.8%) combination therapy. During the course of the study, 42.3% of CTEPH patients underwent PEA. There was a significant improvement of WHO FC ($p<0.003$), mean 6MWD ($p=0.003$), mPAP ($p=0.002$), and PVR ($p=0.008$) for the overall study population; no significant changes were observed in RAP and CI for either the overall population or sub-group analysis. During the follow-up period, a total of 28 (27.7%) patients died of PH-related causes; their median survival time from diagnosis was 3.1 years and only 17.9% of them were under triple combination therapy. For the overall study cohort, 1-, 3-, and 5-year survival was estimated at 86.6%, 76.7%, and 64.1%, respectively. Survival was significantly better for patients ≤40 years old and women with I/HPAH. Survival estimates for the overall cohort and the PAH subgroup followed the trends of the most relevant international cohorts, while survival estimates

were lower than comparable studies for the CTEPH subgroup, which could be connected to difficulties in accessing PEA surgery.

Given the importance of treatment innovations—new drugs and strategies—that occurred in recent decades, we conducted a study to compare treatment outcomes in different periods (2005-2010 vs. 2011-2016) in a PH reference center in Porto, Portugal. *"Long-term Survival in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: Insights From a Referral Centre in Portugal",*[89] was published in Portuguese Journal of Cardiology (2018). In this study, involving 142 patients, 5-year survival estimates tended to improve over time for overall group 1 (67% vs 74%), mainly for CTD-PAH (33 vs 67%) and for CTEPH patients (77% vs 84%), but not for I/HPAH (84 vs 75%). Other relevant findings included: 1) at diagnosis most of the patients were in advanced WHO FC (62% in III/IV FC); 2) the mean age at diagnosis of I/HPAH patients increased over time (54±18 vs 39±15 years); 3) specific treatments used and survival estimates are comparable to other registries and cohort studies; and 4) PEA and lung transplantation were underused treatments despite being associated with better survival of CTEPH and PAH patients. To further improve prognosis, use of parenteral prostanoids and better access to surgical treatments (PEA and lung transplantation) need to be promoted. These results were highlighted in an editorial by Prof. Marc Humbert, which considered our data important to better perceive this rare disease in a time in which there are increasing efforts to better understand rare diseases in Europe, the reason why the European Commission launched the European Reference Networks for rare and low prevalence complex diseases. The contribute of the Portuguese PH research community developing a dedicated information system for PH was also emphasized in this editorial.[94]

## 3.1. Pulmonary Hypertension in Portugal: First Data from a Nationwide Registry

***By Rui Baptista, José Meireles, Ana Agapito, Graça Castro, António Marinho da Silva, Teresa Shiang, Fabienne Gonçalves, Susana Robalo-Martins, António Nunes-Diogo, and Abílio Reis***

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*Clinical Study*

# Pulmonary Hypertension in Portugal: First Data from a Nationwide Registry

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*Introduction*. Pulmonary arterial hypertension (PAH) is a rare disease that must be managed in specialized centers; therefore, the availability of epidemiological national data is critical. *Methods*. We conducted a prospective, observational, and multicenter registry with a joint collaboration from five centers from Portugal and included adult incident patients with PAH or chronic thromboembolic pulmonary hypertension (CTEPH). *Results*. Of the 79 patients enrolled in this study, 46 (58.2%) were classified as PAH and 33 patients (41.8%) as CTEPH. PAH patients had a mean age of 43.4 ± 16.4 years. Idiopathic PAH was the most common etiology (37%). At presentation, PAH patients had elevated right atrial pressure (RAP) (7.7 ± 5.9 mmHg) and mean pulmonary vascular resistance (11.4 ± 6.5 Wood units), with a low cardiac index (2.7 ± 1.1 $L \cdot min^{-1} \cdot m^{-2}$); no patient was under selective pulmonary vasodilators; however, at follow-up, most patients were on single (50%), double (28%), or triple (9%) combination vasodilator therapy. One-year survival was 93.5%, similar to CTEPH patients (93.9%), that were older (60.0 ± 12.5 years) and had higher RAP (11.0 ± 5.2 mmHg, $P = 0.015$). *Conclusions*. We describe for the first time nationwide data on the diagnosis, management, and prognosis of PAH and CTEPH patients in Portugal. Clinical presentation and outcomes are comparable with those reported on other national registries.

## 1. Introduction

In the past few decades, the international scientific community has made great progresses in the understanding of the epidemiology, pathophysiology, and management of pulmonary arterial hypertension (PAH). It is a rare disease, malignant in character, and rapidly fatal, if not treated, with a median survival of 2.8 years in a historic cohort [1]. These progresses were accompanied by the development of drugs that target specific pathways in the pathophysiology of the disease [2]. Management in specialized centers and the use of pulmonary vasodilators lead to a significant impact on the survival and quality of life of PAH patients [3]. Unfortunately, survival rates are still unsatisfactory [4], signaling for the need of more effective treatments, which are under development [5].

Since the first consensus conference in 1973 [6], the classification of pulmonary hypertension (PH) has evolved, reflecting the ongoing understanding of the condition, and now it includes five groups with several subtypes [7]. Within group 1 PH, an idiopathic subgroup is maintained, highlighting that there is still a lot to understand about the pathogenesis of the disease. The diagnostic and therapeutic approach should be guided by national and international guidelines supported by scientific societies, and given the rarity and severity of the disease, its proper investigation and treatment should be performed in expert centers [8, 9].

Chronic thromboembolic pulmonary hypertension (CTEPH), classified as group 4 PH, has a different pathophysiology and treatment from other PH groups. Pulmonary endarterectomy (PEA) is a potentially curative procedure for CTEPH [10]. For those patients not eligible for surgery or those with persistent PH after PEA, specific treatment may ameliorate symptoms and enhance survival [9, 11].

The organization and publication of national and international registries are essential in the understanding of the epidemiology, etiology, and natural history of the different groups of PH [3]. Several groups have published data from their cohorts [12–17], although with different inclusion and exclusion criteria and methodologies [16]; to overcome these disparities, the creation of an international registry has been suggested [18]. Moreover, it is unclear if data from regional registries can be applied to other populations [13]. Data from national registries are not a surrogate for application in other countries and cannot be easily extrapolated due to demography, treatment availability, and other regional differences. Therefore, national registries from each region are paramount in the interpretation of the applicability of international recommendations, which are issued regardless of those differences. Our aim is to present data from a Portuguese registry of patients with group 1 and group 4 PH and to compare them with other published cohorts.

## 2. Population and Methods

We conducted a prospective, observational, and multicenter registry with a joint collaboration from five PH centers around Portugal. Although there are small differences between the institutions regarding patient follow-up, all of them follow similar protocols, according to the published national [8] and international [19] guidelines. Our study population consisted of adult incident PH patients referred to those centers for diagnostic and therapeutic evaluation, between 2008 and 2010. Data were collected by clinical file review by a physician, with supervision from the assistant PH physician, and were compiled in a dedicated software, specifically developed for the management of PH patients (PAHTool, Inovultus, Santa Maria da Feira, Portugal), creating a database and the backbone for a national registry. An informed consent was obtained from each patient, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The centers' participation in this registry was voluntary, and the nationwide data collection was approved by the National Center for Data Protection.

To enable comparisons with other published registries, we used strict inclusion and exclusion criteria. All patients had PAH confirmed by right heart catheterization (RHC), with a mean pulmonary arterial pressure (PAP) over 25 mmHg and a pulmonary wedge pressure (PCWP) equal or under 15 mmHg or a left ventricular end diastolic pressure (LVEDP) equal or under 15 mmHg. The date of diagnosis corresponds to the confirmation of PAH by RHC.

Studied data included demographic characteristics, clinical and laboratorial parameters, World Health Organization (WHO) functional class, haemodynamics, and conventional and specific vasodilator therapy usage and survival status. Vasoreactivity testing was performed when possible, using various institutional protocols. A one-year follow-up was conducted; no patients were lost to follow-up.

All results are expressed as the mean ± standard deviation or as the frequency. We used Kolmogorov-Smirnov for testing normality, Student's $t$-test for continuous variables, and $X^2$-test for categorical variables. Survival analysis was performed using the Kaplan-Meier method, and comparisons were made using the Log-Rank test. Values of $P < 0.05$ were considered to be significant. Statistical analysis was performed using SPSS 17.0 software package (IBM, New York, USA).

## 3. Results

Our registry originally included 188 PH patients (Figure 1). After exclusion of 79 patients from groups 2, 3, and 5 PH, 134 patients were left for analysis. Thirty patients were excluded as they did not have an available RHC. The final analysis included 79 patients. Of the 79 patients enrolled in this study, 46 (58.2%) patients were classified as PAH and 33 patients (41.8%) as CTEPH.

*3.1. Demographics and Clinical Data.* There was a clear preponderance of women among PAH patients, with a female/male patient ratio of 1.9 : 1. Mean age at diagnosis was 43.4 ± 16.4 years (range, 15 to 77 years) (Table 1). There was no difference among genders regarding age at first medical examination ($P = 0.963$). Among the 46 patients, 9.2% ($n = 11$) were <21 years old, 58.3% ($n = 21$) were 21 to 40 years old, 32.6% ($n = 15$) were 40 to 59 years old, and 17.4% ($n = 8$) were > 61 years old. Patients between 21 and 60 years of age accounted for 87% of all patients.

Idiopathic PAH was present in 17 (37%) patients, followed by connective tissue disease (CTD) ($n = 12$, 26%), congenital heart disease (CHD) ($n = 10$, 22%), portopulmonary hypertension ($n = 5$, 11%), familial ($n = 1$, 2%), and other etiologies ($n = 1$, 2%) (Table 2). At baseline, most patients presented in WHO class III or IV (71%); only one patient was in class I.

CTEPH patients had a higher mean age at diagnosis (60.3 ± 12.5, $P < 0.001$) than group 1 PAH patients; a significant proportion of the population had more than 51 years at diagnosis (63.6%) (Figure 2). Both WHO class at presentation and the female/male ratio were similar to group 1 PAH patients.

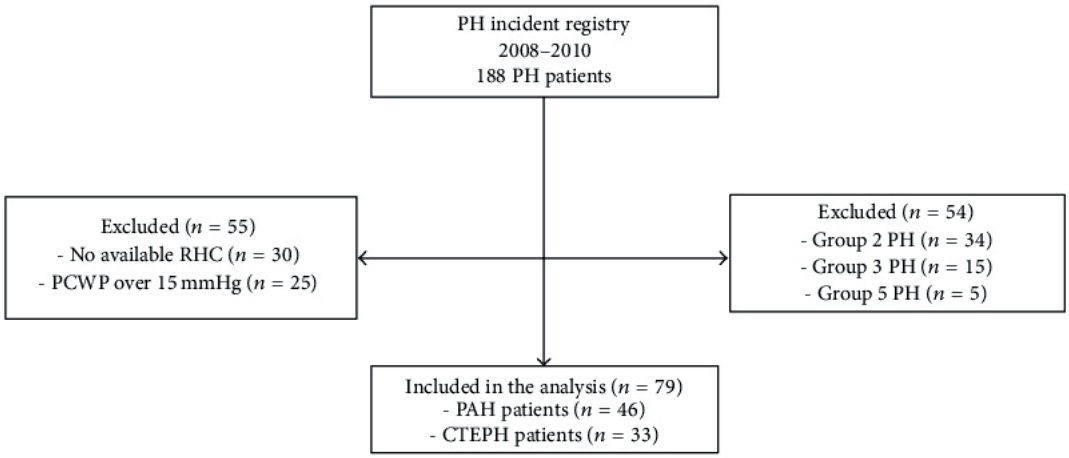


FIGURE 1: Patient selection flowchart.

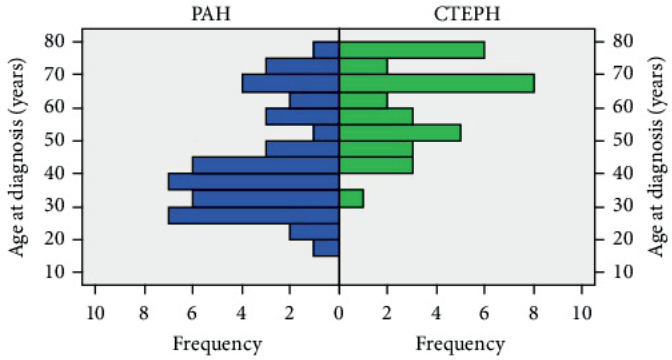


FIGURE 2: Distribution of age and gender.

*3.2. Hemodynamics.* RHC was performed in all patients at the initial examination (Table 1). Baseline data shows that in group 1 PAH patients, mean RAP was 7.7 ± 5.9 mmHg, mean PAP was 50.6 ± 17.9 mmHg, and mean PCWP was 9.5 ± 3.5 mmHg; PVR was 11.4 ± 6.5 Wood units. Mean cardiac output (CO) was 4.5 ± 1.8 L·min$^{-1}$, and mean cardiac index (CI) was 2.7 ± 1.1 L·min$^{-1}$·m$^{-2}$. Cardiac output was more elevated in WHO class I/II than in the WHO class III or IV patients, but it did not reach statistical significance. Conversely, PVR was higher in patients in WHO class III/IV than patients in WHO class I/II (Table 3). Vasoreactivity testing was performed in 29 (63.0%) patients with various protocols; 6 patients (21%) had a positive test.

Regarding CTEPH, the only hemodynamic parameter at the time of diagnostic RHC that was significantly different from PAH was the mean RAP (11.0 ± 5.2 mmHg, $P$ = 0.015), that was significantly higher.

*3.3. Treatment.* Drug therapy at study inclusion is shown in Table 4. At baseline, all PAH patients were treated only with conventional therapy. Diuretics were used by 15 patients (32.6%), followed by oxygen in 9 patients (19.6%) and digoxin in 7 patients (15.2%). At follow-up, 42 patients were treated with advanced PAH therapies and 40 with pulmonary vasodilators, and two patients were enrolled in randomized controlled trials (RCT) (Table 5). Most patients were medicated with endothelin receptor antagonists ($n$ = 33), followed by phosphodiesterase inhibitors ($n$ = 26) and prostanoids ($n$ = 4). Thirteen patients (28%) were under double combination therapy and 4 (9%) patients under triple combination therapy.

No differences were found regarding baseline treatment modalities among PAH and CTEPH patients. However, during follow-up, targeted therapies were begun in 67% of CTEPH patients, and 5 patients (15.2%) had a PEA. Combination therapy was offered to 9 CTEPH patients during the follow-up period. Endothelin receptor antagonists were used in 17 patients, followed by sildenafil in 13 patients and prostanoids in 2 patients. One patient was enrolled in a RCT.

*3.4. One-Year Survival Analysis.* Survival data was available for all patients (Figure 3). One year after the diagnostic RHC, 5 patients were deceased. The Kaplan-Meier survival estimates for patients with PAH and CTEPH at 1 year were 93.5% and 93.9%, respectively (Log-rank $P$ = 0.709). Unoperated CTEPH patients had a one-year survival rate of 92.9%, whereas all patients that underwent PEA survived.

*3.5. Comparison with the Cohort of Group 1 PAH Patients without Available Baseline RHC.* The original database included

Table 1: Demographic, clinical, and hemodynamic characteristics of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) incident patients at baseline.

| | Total ($n = 79$) | PAH ($n = 46$) | CTEPH ($n = 33$) | $P$ value |
|---|---|---|---|---|
| Age (years) | 50.5 ± 17.0 | 43.4 ± 16.4 | 60.3 ± 12.5 | <0.001 |
| Female gender, $n$ (%) | 53 (67.1%) | 30 (65.2%) | 23 (69.7%) | 0.676 |
| Six-minute test walking distance (m) | 351.3 ± 137.4 | 370.8 ± 140.1 | 320.4 ± 132.9 | 0.327 |
| Functional class, $n$ (%) | | | | |
| I | 1 (1%) | 1 (2%) | 0 (0%) | 0.565 |
| II | 17 (25%) | 11 (27%) | 6 (21%) | |
| III | 34 (49%) | 21 (51%) | 13 (46%) | |
| IV | 17 (25%) | 8 (20%) | 9 (32%) | |
| Hemodynamic data | | | | |
| Right atrial pressure (mmHg) | 9.1 ± 5.8 | 7.7 ± 5.9 | 11.0 ± 5.2 | 0.015 |
| Mean pulmonary artery pressure (mmHg) | 49.1 ± 15.1 | 50.6 ± 17.9 | 47.1 ± 9.9 | 0.313 |
| Cardiac output ($L \cdot min^{-1}$) | 4.4 ± 1.9 | 4.5 ± 1.8 | 4.3 ± 2 | 0.778 |
| Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$) | 2.6 ± 1.1 | 2.7 ± 1.1 | 2.5 ± 1.1 | 0.406 |
| Pulmonary capillary wedge pressure (mmHg) | 9.7 ± 3.3 | 9.5 ± 3.5 | 9.9 ± 3.1 | 0.587 |
| Pulmonary vascular resistance (Wood units) | 11.1 ± 6.4 | 11.4 ± 6.5 | 10.8 ± 6.3 | 0.729 |

Table 2: Clinical and hemodynamic data stratified by pulmonary arterial hypertension subgroup.

| Subgroup | $N$ (%) | Female (%) | Age (years) | WHO I/II (%) | 6MWT (meters) | RAP (mmHg) | mPAP (mmHg) | CO ($L \cdot min^{-1}$) | PCW (mmHg) | PVR (WU) |
|---|---|---|---|---|---|---|---|---|---|---|
| Idiopathic | 17 (37.0) | 70.6 | 37.5 ± 12.9 | 31.3 | 405 ± 121 | 11 ± 6 | 53 ± 15 | 4.2 ± 1.5 | 10.7 ± 3.3 | 11.7 ± 5.6 |
| CTD | 12 (26.1) | 75.0 | 56.8 ± 12.4 | 27.3 | 275 ± 127 | 6 ± 6 | 39 ± 11 | 4.9 ± 1.8 | 7.6 ± 3.2 | 8.7 ± 7 |
| CHD | 10 (21.7) | 50.0 | 37.7 ± 15 | 22.2 | 351 ± 171 | 6 ± 5 | 60 ± 27 | 4.6 ± 2.7 | 10.7 ± 3.7 | 13.9 ± 8.9 |
| PortPulm | 5 (10.9) | 60.0 | 51.2 ± 18.3 | 33.3 | n/d | 7 ± 5 | 51 ± 11 | 4 ± 1.2 | 8.6 ± 2.9 | 11.1 ± 3.3 |
| Total | **44 (100.0)*** | 65.2 | 43.4 ± 16.4 | 29.3 | 371 ± 140 | 8 ± 6 | 51 ± 18 | 4.5 ± 1.8 | 9.5 ± 3.5 | 11.4 ± 6.5 |

CTD: connective tissue disease; CHD: congenital heart disease; PortPulm: portopulmonary. WHO: World Health Organization; 6MWT: six-minute walking test distance; RAP: right atrial pressure; mPAPA: mean pulmonary artery pressure; CO: cardiac output; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; WU: wood units.
*Heritable PAH ($n = 1$) and other etiologies PAH ($n = 1$) were not reported as there was one case of each in the cohort.

Table 3: Hemodynamic characteristics stratified by NYHA class of pulmonary arterial hypertension incident patients.

| ($n = 46$) | NYHA I/II | NYHA III | NYHA IV | $P$ value |
|---|---|---|---|---|
| Six-minute walk test distance (m) | 436 ± 147 | 356 ± 106 | 236 ± 128 | 0.094 |
| Female gender | 67.8% | 71.4% | 37.5% | 0.229 |
| Right atrial pressure (mmHg) | 8 ± 6 | 8 ± 6 | 7 ± 7 | 0.854 |
| Mean pulmonary artery pressure (mmHg) | 54 ± 26 | 49 ± 11 | 45 ± 13 | 0.492 |
| Pulmonary capillary wedge pressure (mmHg) | 9 ± 3 | 10 ± 4 | 7 ± 3 | 0.092 |
| Cardiac output ($L \cdot min^{-1}$) | 5.4 ± 0.9 | 4.6 ± 2.1 | 3.2 ± 1.6 | 0.097 |
| Pulmonary vascular resistance (Wood units) | 9.1 ± 4.6 | 10.6 ± 5.6 | 15.3 ± 6.1 | 0.123 |

Table 4: Conventional therapies at baseline and follow-up of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients.

| | Total | | PAH | | CTEPH | |
|---|---|---|---|---|---|---|
| | Baseline | Follow-up | Baseline | Follow-up | Baseline | Follow-up |
| Diuretics | 33 (41.8%) | 40 (65.6%) | 15 (32.6%) | 17 (60.7%) | 18 (54.5%) | 23 (69.7%) |
| Digoxin | 13 (16.5%) | 18 (2.8%) | 7 (15.2%) | 11 (23.9%) | 6 (18.2%) | 7 (21.2%) |
| Oxygen | 21 (26.6%) | 25 (31.6%) | 9 (19.6%) | 12 (26.1%) | 12 (36.4%) | 13 (39.4%) |
| Warfarin | 34 (43.0%) | 59 (74.7%)* | 10 (21.7%) | 28 (60.9%)* | 24 (72.7%) | 31 (93.9%)* |

*$P < 0.001$ versus baseline.

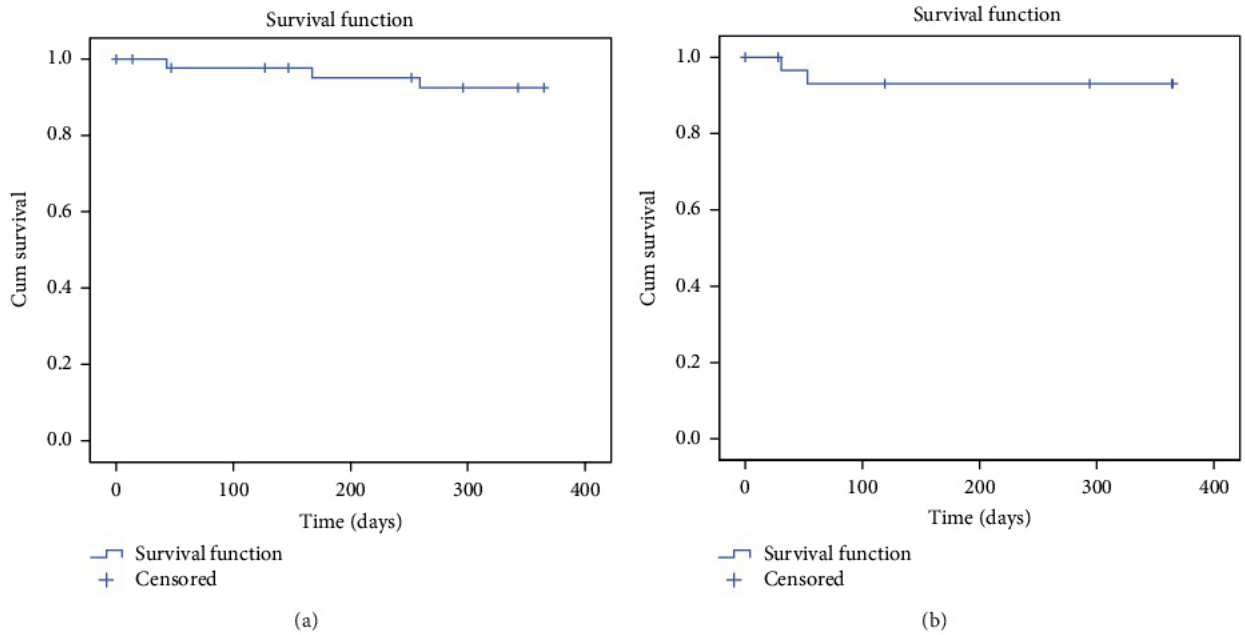


Figure 3: One-year survival in pulmonary arterial hypertension (a) and chronic thromboembolic pulmonary hypertension (b) patients.

Table 5: Pulmonary vasodilator therapies at follow-up of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients.

| | PAH | CTEPH |
|---|---|---|
| No advanced therapies | 2% | 33% |
| Single therapy | 50% | 36% |
| Double combination therapy | 28% | 15% |
| Triple combination therapy | 9% | 7% |
| Calcium channel blockers | 7% | 0% |
| Randomized controlled trial drug | 4% | 3% |

20 patients classified as PAH but without an available baseline RHC; therefore, they were not included in the analysis. This may have been due to the incomplete filling of the database fields and thus not necessarily reflecting the absence of RHC. Comparing with included PAH patients, we found no significant differences regarding gender, age, or WHO class at presentation of these patients. Although not reaching statistical significance, there was a trend for a higher proportion of patients with CHD-associated PAH in the group of patients that did not had a RHC. No survival differences were found among the two groups.

*3.6. Estimated Incidence of PAH and CTEPH.* Although limited by the voluntary collection of data and by the selective inclusion and exclusion criteria, we identified 46 patients with incident group 1 PAH and 33 patients with CTEPH during the 3-year follow-up period. For a population of 10 million inhabitants in Portugal, we calculated a conservative estimation of group 1and group 4 PH annual incidence of at least 1.5 and 1.1 patients per million, respectively. However, if we include patients with a clinical diagnosis of group 1 PAH but without an available RHC, our incidence would rise to 2.2 per million per year.

## 4. Discussion

The present study summarizes data representative of the Portuguese PH cohort. With the combined effort of five treatment centers, we were able for the first time to collect nationwide data on the diagnosis, management, and clinical course of PAH and CTEPH in Portugal.

To analyze a homogeneous population and to enable comparisons with other published cohorts [12, 17, 20], we followed strict inclusion and exclusion criteria based on current guidelines [9]. We focused only on PAH and CTEPH patients, as the prevalence and clinical characteristics of group 2 and group 3 PH varied widely among the five PH centers. Additionally, we included only incident cases to remove survivor bias from our study and to permit an approximate calculation of annual incidence, as prevalent cases correspond mainly to survivors [12].

In our PAH population, age at diagnosis was lower than in the REVEAL [20] and French [12] cohorts but higher than in the NIH registry [21]. This may be due to the fact that one-fifth of our patients had CHD-associated PAH; these patients were excluded from the French registry [12] but not from the REVEAL cohort [20]. Other important aspect is that almost 20% of PAH patients were over 60 years, a finding that is being increasingly recognized in contemporary registries. CTEPH patients were older, with a mean age at diagnosis of 60 years, similar to the one found in the Swiss cohort [22] and the randomized clinical trial [23]. Interestingly, our CTEPH population was significantly older than a published cohort of patients developing CTEPH after an acute pulmonary embolism [24]. This fact may warrant further investigation

and may signalize a different epidemiology of postpulmonary embolism CTEPH.

Possibly due to the fact that we have no patients with PAH secondary to anorexigens, a group almost exclusively formed by women [25], the proportion of female patients (65%) in our PAH cohort was lower than that in most published reports [26].

Idiopathic PAH was the most frequent subgroup of PAH, with a proportion of 37%, similar to the French cohort (41% in the incident cohort) [12] but lower than in the REVEAL cohort (47%) [20]. CTD-PAH was the second most common cause, with 26%, a number that is higher than that reported on the French (18%) [12] but similar to the REVEAL cohort (24%) [20]. Systemic sclerosis is the leading cause of CTD-PAH, with 8% of patients developing this dismal prognostic finding in the course of their disease [27]; echocardiographic screening may be of value and has a grade IIb C recommendation on the current ESC guidelines [9].

As expected, patients with CHD-PAH were frequent in our series (22%), a significantly higher proportion than in the French and REVEAL cohorts [12, 20]. This may be the result of the poor access of CHD patients to corrective heart surgery in the appropriate age; however, CHD patients are also clearly underrepresented in other epidemiological series, as in the French cohort due to health organization issues [12]. Portopulmonary hypertension had a similar incidence to the French series.

PAH baseline haemodynamics was similar to those from the NIH, REVEAL French Comparison Cohort (FCC), and French registry. The mean PAP was 51 mmHg, being essentially the same of the French registry (55 mmHg) [12] and the REVEAL FCC (51 mmHg) [26] and slightly lower than the NIH cohort (60 mmHg) [1]. Mean RAP at diagnosis was 8 mmHg, the same as the French (8 mmHg) and REVEAL FCC registry (8 mmHg).

Most PAH patients presented to the referral center with symptoms of advanced heart failure. In 71% of cases, they were in WHO class III or IV, similarly to the REVEAL FCC (73%) [26] and the French registry (75%) [12]. This number is even more dramatic as it is similar to the one reported on the 20-year-old NIH cohort (71%) [21]. The combination of high RAP with an advanced functional class on presentation signalizes that more effort is needed for early identification and referral of patients to expert centers, as there is evidence that treating patients in WHO class II has a positive impact on patients' outcomes [28].

CTEPH patients had similar haemodynamics compared to PAH, except for mean RAP, which was significantly higher. This finding that was not reproduced in the Swiss cohort [22], is higher than that reported in the BENEFIT study [23] and in the Cambridge cohort [29]. Higher right ventricular filling pressures were accompanied by a higher number of patients being referred to WHO class III or IV (78%), although similar to the proportion reported in the literature [29]. This may indicate late identification and the referral of these potentially curable patients.

Although having high WHO functional class at presentation, most PAH patients were not treated with diuretics when referred to the expert centers. The same was true regarding CTEPH patients; however, there was a trend for more intense anticongestive medication in this group. Our results are comparable to those from the Swiss registry [22]. Late referral to specialized centers may be in part due to the lack of an nationwide reference network and availability of oral vasodilator drugs for PAH treatment, as less specialized centers may delay transfer patients to expert centers [12]. In our population, no patient was treated with specific pulmonary vasodilators before being referred to the specialized centers.

Vasoreactivity testing was held in 29 of 46 PAH patients (63%) and was positive in 6 patients (21%). This value is significantly higher than that reported by the French cohort (10.3%) [12] but similar to the Swiss registry (20%) [17], although the latter included 8 CTEPH patients. Selection bias, differences in the definition of acute responders and in the treatment protocols used nationwide, may be responsible for the inconsistencies. Publication of national guidelines may help to standardize the care for this group of patients.

The progress in prognosis is inseparable from the advances in pulmonary vasodilator therapy. There are three classes of selective vasodilator drugs that target three critical pathways in PAH (prostacyclin, nitric oxide, and endothelin-1) [2], all being available in Portugal. All of them have their efficacy demonstrated in several randomized controlled trials regarding functional capacity, exercise tolerance, haemodynamics, and other endpoints [30]. Moreover, a recent meta-analysis confirmed the impact of pulmonary vasodilators on short-term survival [11]. Overall, in our cohort the one-year survival for PAH patients was 93.5%, similar to the REVEAL (91.0%) [20] and the Swiss cohort (89.0%) [22] but higher than the French cohort (85.7%) [12]. The differences may be accounted by the small number of events in our cohort (5 deaths) and the relative higher proportion of patients with CHD-associated PAH (21.7%) compared with the REVEAL (11.8%), Swiss (approximately 14.3%), and French cohorts (0%) [12, 17, 20]. These patients clearly have a better prognosis [31], and thus they may have contributed to the positive survival results.

CTEPH patients had a similar one-year survival (93.9%); only five patients underwent PEA, a potentially curative procedure that probably had impact on prognosis, as no patient died on follow-up. All CTEPH patients are assessed by the local medical PH team, and the potential surgical candidates are discussed directly with the foreign referral center, as the procedure was not routinely performed in our country. Not operated patients had a survival of 92.9%. For these patients and for those with residual PH after PEA, pulmonary vasodilator drug therapy is a class IIb C recommendation in the ESC guidelines [9]. In our cohort, two thirds of CTEPH patients started specific therapy, a number that is comparable to other series [29]. Interestingly, the one-year survival of the not operated CTEPH patients was similar to that recently reported in the literature (96%) [32].

Our estimated PAH annual incidence between 1.5 and 2.2 cases per million inhabitants is in line with the published incidences in other countries: Belgium (1.7 per million) [33], Israel (1.4 per million) [34], France (2.4 per million) [12], Switzerland (2.4 per million) [17], and USA (2.0 per million)

[26]. The wide range between the most conservative estimate and the higher value is also observed in other series, as in France, where there are very high regional differences in PAH prevalence, ranging from 5 to 25 per million inhabitants per year [12]. CTEPH had, in our population, an estimated incidence of 1.1 cases per million, a number similar to that reported in the United Kingdom in 2001 (1.02 cases per million) but lower than that in 2005 (1.75 cases per million) [29].

Our study has several limitations. First, although we included data from five expert PH centers in Portugal, there are patients followed in other hospitals across the country. This had impact on incidence calculations, namely, an underestimation of values, both in PAH and CTEPH. Second, we used strict inclusion and exclusion criteria for the recruitment of patients in this registry to ensure a homogenous population. This has caused the exclusion of all patients without a RHC on the databases, whether or not there was one available on the clinical files. However, as our mean hemodynamic values, demographics, and functional class data are in line with those published on the literature, we believe that our population is representative and has external validity. Thirdly, we decided not to include groups 2, 3, and 5 patients, as there were significant differences among centers regarding the clinical characteristics of these patients. A careful analysis was made, but avoiding confounding factors that are frequent in observational studies may have been impossible [35].

In conclusion, the present unique study reports for the first time data on the epidemiology, clinical characteristics, and prognosis of PAH and CTEPH patients in Portugal. We conclude that overall PAH incidence is similar to that reported in other European series, but patients are still being diagnosed late in the course of their disease. We also report that CHD-PAH is an important etiology in our country and may need special attention. The one-year survival analysis of our incident cohort exceeds 93%, a value that reflects access to contemporary treatment of PAH, being a strong incentive to the continuous work being developed by all the community members involved in this disease. We demonstrated that a combined and organized registry is possible and is a useful tool to obtain quality data for clinical decision-making that compares well with data from other registries. Our findings encourage the amplification and maintenance of a nationwide registry by the combined effort of all the physicians caring these patients, aiming for a better care and prognosis of PH patients.

## Conflict of Interests

Abílio Reis is the coproprietary of the dedicated pulmonary hypertension software PAHTool. The remaining authors have no conflict of interests to disclose.

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## 3.2. Pulmonary hypertension: Real-world data from a Portuguese expert referral centre

***By Ana Gomes, Célia Cruz, Joana Rocha, Miguel Ricardo, Margarida Vicente, Alzira Melo, Mário Santos, Luísa Carvalho, Fabienne Gonçalves, and Abílio Reis***

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ORIGINAL ARTICLE

# Pulmonary hypertension: Real-world data from a Portuguese expert referral centre

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**KEYWORDS**
Pulmonary hypertension;
Pulmonary arterial hypertension;
Survival;
Portuguese population;
Cohort;
Real-world data

**Abstract**
*Background:* Pulmonary hypertension (PH) is a heterogeneous, debilitating condition with highly relevant impact on functional capacity, quality of life, and life-expectancy.
*Objectives:* This study aims to provide long-term data on the Portuguese PH population, by characterising the clinical presentation, evolution, and outcomes of PH patients in a specialised referral centre.
*Methods:* Retrospective analysis of a cohort of 101 patients with pre-capillary PH (pcPH) referenced to an expert tertiary care referral centre in northern Portugal from 2002 to 2013. Diagnosis was confirmed by right heart catheterisation (RHC). PH classification followed consensus criteria from the 5th World Symposium in Nice, 2013.
*Results:* The most frequent causes of pcPH were Group 1 PH – pulmonary arterial hypertension (PAH) (54.4%) and Group 4 PH – Chronic thromboembolic pulmonary hypertension (CTEPH) (25.7%); importantly, 17.8% of patients presented PH associated with multiple aetiologies. Targeted therapy was used in 91.1% of patients (48.5% combination therapy). 1-, 3-, and 5-year survival was estimated at 86.6%, 76.7%, and 64.1%, respectively. Survival was significantly better for those 40 years old (10.5 vs. 6.4 years; $P = 0.003$) and for women with I/HPAH (9.3 vs. 4.5 years; $P = 0.039$).

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*Conclusions:* This study provides long-term, real-world data for the management of PAH and CTEPH in Portugal and demonstrates the importance of dedicated electronic medical records and well defined clinical management protocols for better patient outcomes. Patients presented mostly with intermediate or high risk of mortality, which suggests delayed diagnosis and highlights the need to increase awareness among clinicians.


## Introduction

Pulmonary hypertension (PH) is an heterogeneous condition associated with various underlying disorders, which is defined as at rest mean pulmonary arterial pressure (mPAP) 25 mmHg confirmed by right heart catheterisation (RHC).[1] The pathophysiological processes associated with the development of PH are complex and more than likely multifactorial, why explains why several types of classification have been proposed over the years. The most recent international consensus from the 5th World Symposium held in Nice in 2013, classifies PH according to five general groups of aetiologies.[2] Group 1 PH refers to pulmonary arterial hypertension (PAH) and includes idiopathic pulmonary arterial hypertension (IPAH), heritable pulmonary arterial hypertension (HPAH), and drugs and toxin induced; PH associated with diseases such as connective tissue disease (CTD), HIV infection, portal hypertension, congenital heart disease (CHD) and schistosomiasis are also included in Group 1. Group 1 and Group 1 refer to pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis and persistent pulmonary hypertension of the newborn, respectively. Group 2 PH includes PH due to left heart disease (LHD). Group 3 refers to PH due to lung diseases or hypoxia, such as chronic obstructive pulmonary disease (COPD) or interstitial lung disease. Group 4 PH includes chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions. Group 5 refers to PH with unclear and/or multifactorial mechanisms.

Group 1 (PAH) aetiologies, except schistosomiasis associated PAH, are considered rare diseases; IPAH being an exclusion diagnosis, is the most studied form of PAH and the model for clinical management of PAH forms which are indicated for targeted therapy.[3,4] Treatment of PH involves both conventional, symptom-based therapy and targeted therapy, which is indicated for specific PH aetiologies. Conventional treatment involves the use of digoxin to improve right ventricular function, diuretics to reduce peripheral oedema, supplemental oxygen, and in specific cases anticoagulants.[3] Calcium channel blockers (CCBs) can be used to lower PAP, but their use is restricted to a small percentage of patients (3–5%) showing positive response to acute pulmonary vasodilator (ARVT) challenge.[5,6] Targeted therapy includes the use of endothelin-1 receptor antagonists (ERA),[7–9] phosphodiesterase-5 inhibitors (PDE-5I),[10,11] soluble guanylate cyclase (sGC) stimulators,[12,13] and prostacyclin analogues or receptor agonists,[14–19] surgical treatment, like lung or heart-lung transplantation is reserved to refractory cases of PAH; pulmonary angioplasty and pulmonary endarterectomy is reserved to CTEPH patients.

The proliferation of studies assessing long-term prognosis of PH has helped identify considerably different patients and disease characteristics both over time and for populations in different geographical regions.[20] These findings suggest the need for specific regional data, to fully characterise local disease populations, inform clinical practice, and to help define local/regional political strategies.

In Portugal, a national PH registry has been, but given its recent implementation, only short-term data have been published.[21] Recently, another study characterised the survival over a longer follow-up period but the sample size remained relatively small ($n = 66$).[22]

This study aims to provide long-term data for the Portuguese PH population, by characterising the clinical presentation, evolution, and outcomes of PH patients in a specialised referral centre in Portugal.

## Materials and methods

### Study population

We conducted a retrospective analysis of a cohort of PH patients referenced to an expert tertiary care referral centre in northern Portugal (Pulmonary Vascular Disease Unit, Centro Hospitalar do Porto – Hospital de Santo António, Porto, Portugal) from 2002 to 2013. At this centre, patients followed a defined protocol for the clinical management of PH, which was adjusted to the applicable national[23] and international guidelines during the period of the study. The protocol specified mandatory clinical assessments, which were prospectively collected in dedicated PH software developed by the centre (PAHTool®, Inovultus Lda, Santa Maria da Feira, Portugal).

PH was confirmed by right heart catheterisation (RHC), with a mean pulmonary artery pressure (mPAP) 25 mmHg; pulmonary arterial wedge pressure (PAWP) 15 mmHg was used to define pre-capillary PH. For the purposes of this study, clinical classification of PH followed standard criteria according to the consensus from the 5th World Symposium in Nice, 2013. Patients with left heart disease (LHD) (Group 2 PH) were not included in this study, due to the

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significantly different pathophysiology, treatment approaches, and prognosis.

The study was approved by the ethics committee of Hospital de Santo António, Porto, Portugal. All patients provided their written informed consent prior to enrolment in the study.

### Medical care

Patients received standard medical care throughout the period of the study. Treatment was prescribed by the accompanying physician based on national and international guidelines applicable at time of the study (as defined in the protocol implemented at the centre) and local treatment availability. Overall, all patients received standard conventional treatment when clinically indicated, including anticoagulants, diuretics, digoxin, oxygen supplementation, and high dose calcium channel blockers (CCBs) (if they were AVRT responders). Selected patients received molecular targeted therapy in addition to conventional therapy, including endothelin-1 receptor antagonists (ERA), phosphodiesterase-5 inhibitors (PDE-5I), and prostacyclin analogues.

### Assessments

Demographic characteristics (gender and age) and clinical characteristics (PH aetiology, symptoms, WHO functional class, 6-min walking test (6MWT), N-terminal pro brain natriuretic peptide (NT-proBNP), and haemodynamic parameters) were collected at baseline. According to the protocol implemented at the centre, patients attended, routinely, 3–4 visits per year or if they had any sign of deterioration. During follow-up the following assessments were considered mandatory: type of treatment administered, clinical evaluation focused on signs of deterioration (like heart failure or syncope), WHO functional class, 6MWT, and NT-proBNP; and yearly haemodynamic re-evaluation. Survival was established based on the electronic medical records (EMR).

### Statistical methods

Demographic and clinical variables were summarised with descriptive statistics. Categorical variables were summarised as absolute frequency and percentage, whereas continuous variables were summarised as mean and standard deviation (SD). Student's *t*, Wilcoxon's, Fisher's exact, or chi-square tests were used to conduct paired/independent univariate/bivariate analysis as appropriate. Cumulative survival was estimated using the Kaplan–Meier method. Patients were censored at the end of the study, except for those who underwent lung transplantation, censored at the time of transplantation. Differences between the survival curves (according to baseline characteristics and disease aetiology) were analysed using the log-rank test. A 5% significance level was employed for all analyses. For the purpose of subgroup analysis patients with multiple aetiology were excluded from any subgroup analysis, except those for whom CTEPH was considered their main diagnosis.

Data was retrieved from PAHTool®. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

## Results

### Study population and baseline characteristics

During the enrolment period of the study, a total of 211 patients with suspected PH were referenced to the Pulmonary Vascular Disease Unit (PDVU). RHC confirmed PH in 120 patients, of which, 19 were excluded from the analysis (10 patients lost to follow-up and 9 patients with exclusive left heart disease), leading to a final study cohort of 101 patients with pcPH. The majority of patients represented incident cases ($n = 81$, 80.2%), however, 20 (19.8%) patients had a prior diagnosis of congenital heart diseases before referral, having started specific therapy at admission to the centre. Fig. 1 presents the patient disposition in the study cohort.

The mean SD follow-up time in the overall study population was 3.8 2.7 years. Table 1 presents the baseline demographic and clinical characteristics of the study population. Approximately 66.3% of patients were female (3:1 ratio) and the mean SD age at baseline was 49.6 19.6 years. Most participants showed moderate to severe disease manifestations at baseline, with 60.4% of patients presenting in WHO functional classes (FC) III or IV, with a mean NT-proBNP level of 1533.4 1758.3 pg/mL, and walking a mean distance of 319.6 132.9 m on 6MWT. Haemodynamically, patients showed increased mPAP of 48.5 16.5 mmHg, increased PVR of 8.1 4.8 wood units, increased RAP 11.1 5.3 mmHg, and normal CI of 3.0 1.1 L/min.

The most frequent causes of PH were Group 1 PH – PAH (54.4%) and Group 4 PH – CTEPH (25.7%); from the PAH subgroup, CHD (36.3%) was the most frequent, followed by I/HPAH (32.7%), and CTD (20.0%); importantly, 17.8% of patients presented PH of multiple aetiology.

Concerning the most frequent PH subgroups, I/HPAH and CHD patients were younger ($P < 0.001$); for all subgroups of aetiologies most patients presented with WHO FC III/IV, but patients with CHD and CTEPH showed significantly ($P < 0.001$) worst functional capacity at baseline.

### Treatment and clinical evolution

Table 2 shows PH treatment used at the last follow-up visit. All patients received conventional treatment during the period of the study, with 8.9% of those receiving conventional therapy only. Targeted therapy was used with 91.1% of participants in addition to conventional therapy. 4 (6.8%) I/HPAH patients were AVRT responders, but only 2 were long-term responders, being treated with high doses of CCBs only.

Single targeted therapy was used in 42.6% of patients, dual combination therapy in 29.7%, and triple combination therapy in 18.8%. 42.3% of CTEPH patients underwent pulmonary endarterectomy during the course of the study. The majority of patients with I/HPAH were under combination therapy (88.9%), with 61.1% under triple therapy. Most patients with CTD (54.4%) and CHD (55.0%) were

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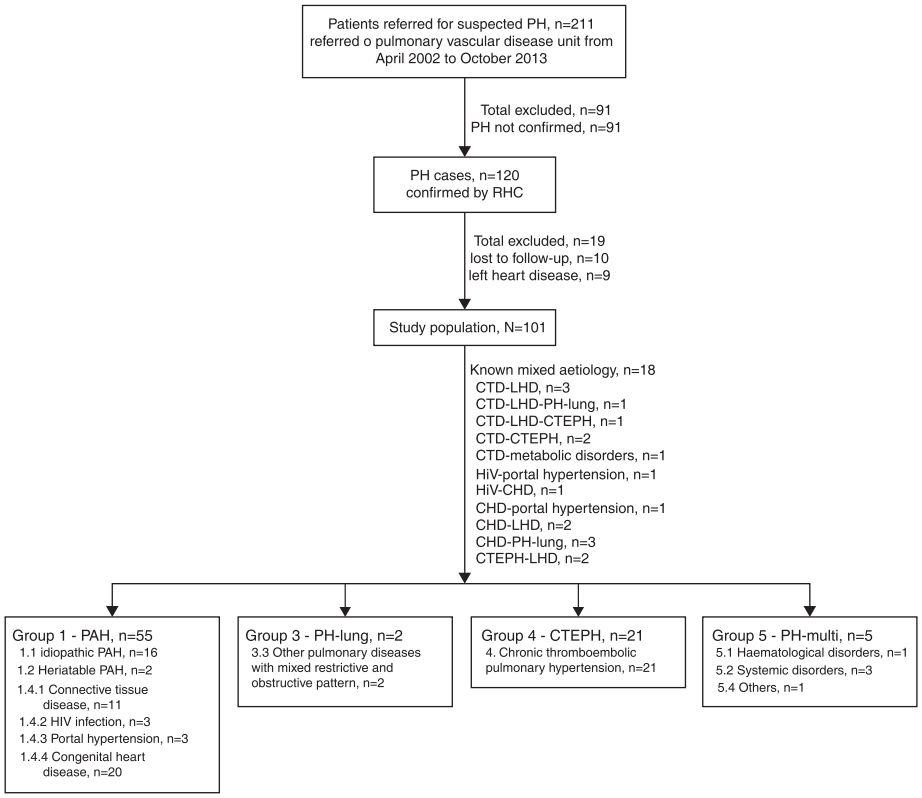


**Figure 1** The study cohort. PH: pulmonary hypertension; RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; PH-lung: pulmonary hypertension associated with lung disease; CTEPH: chronic thromboembolic pulmonary hypertension; PH-misc: miscellaneous pulmonary hypertension.

**Table 1** Baseline demographic and clinical characteristics.

| | Overall ($n=101$) | I/HPAH ($n=18$) | CTD ($n=11$) | CHD ($n=20$) | CTEPH ($n=26$) | *P*-value |
|---|---|---|---|---|---|---|
| *Age, years* | 49.6 19.6 | 36.4 14.9 | 56.6 4.7 | 35.3 5.2 | 60.1 14.0 | <0.001 |
| *Female, n (%)* | 67 (66.3) | 12 (66.7) | 9 (81.8) | 11 (55.0) | 18 (69.2) | 0.466 |
| *WHO FC, n (%)* | | | | | | |
| I/II | 40 (39.6) | 9 (50.0) | 6 (45.5) | 6 (30.0) | 8 (30.7) | 0.220 |
| III/IV | 61 (60.4) | 9 (50.0) | 5 (54.5) | 14 (70.0) | 18 (69.3) | |
| *6MWT, m* | 319.6 132.9 | 360.7 117.5 | 297.3 53.6 | 330.7 24.1 | 289.4 144.3 | 0.380 |
| *NT-proBNP, pg/mL* | 1533.4 1758.3 | 1543.8 1712.6 | 2081.9 909.8 | 1139.3 277.4 | 2163.8 1805.5 | 0.349 |
| *Haemodynamics* | | | | | | |
| mPAP, mmHg | 48.5 16.5 | 56.9 17.7 | 38.3 3.3 | 77.6 7.8 | 44.6 7.7 | <0.001 |
| PAWP, mmHg | 11.1 5.3 | 10.8 5.2 | 7.6 0.9 | 19.0 2.1 | 9.79 4.81 | 0.002 |
| RAP, mmHg | 8.2 4.6 | 9.6 5.2 | 4.6 0.5 | 5.0 1.0 | 8.9 5.4 | 0.092 |
| CO, L/min | 5.2 1.8 | 4.7 1.7 | 5.3 0.6 | 5.0 1.2 | 4.73 1.22 | 0.739 |
| CI, L/min | 3.0 1.1 | 2.9 1.2 | 3.0 0.3 | 3.3 0.4 | 2.72 0.71 | 0.739 |
| PVR, WU | 8.1 4.8 | 11.4 6.7 | 6.1 0.9 | 13.2 3.4 | 7.87 2.65 | 0.076 |

Results are presented as mean SD, except when otherwise indicated.
IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; CTD: connective tissue disease; CHD: congenital heart disease; CTEPH: chronic thromboembolic pulmonary hypertension; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro brain natriuretic peptide; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; RAP: right atrial pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance.

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**Table 2** Medical and surgical treatment at the last follow-up visit.

| Treatment | Overall($n$ = 101) | I/HPAH($n$ = 18) | CTD($n$ = 11) | CHD($n$ = 20) | CTEPH($n$ = 26) |
|---|---|---|---|---|---|
| *Single targeted treatment* | | | | | |
| Patients under monotherapy only | 43 (42.6) | 3 (16.7) | 4 (36.4) | 9 (45.0) | 15 (57.7) |
| PDE-5I | 5 (5.0) | 0 (0.0) | 0 (0.0) | 1 (5.0) | 3 (11.5) |
| ERA | 38 (37.6) | 3 (16.7) | 4 (36.4) | 8 (40.0) | 12 (46.2) |
| *Combination treatment* | | | | | |
| Patients under combination therapy | 49 (48.5) | 16 (88.9) | 6 (54.5) | 11 (55.0) | 11 (42.3) |
| Dual combination therapy | 30 (29.7) | 5 (27.8) | 4 (36.4) | 9 (45.0) | 8 (30.8) |
| Triple combination therapy | 19 (18.8) | 11 (61.1) | 2 (18.2) | 2 (10.0) | 3 (11.5) |
| PDE-5I + Prostanoids | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Prostanoids + ERA | 9 (8.9) | 2 (11.1) | 1 (9.1) | 1 (5.0) | 4 (15.4) |
| PDE-5I + ERA | 21 (20.8) | 3 (16.7) | 3 (27.3) | 8 (40.0) | 4 (15.4) |
| PDE-5I + Prostanoids + ERA | 19 (18.8) | 11 (61.1) | 2 (18.2) | 2 (10.0) | 3 (11.5) |
| *Surgical treatment* | | | | | |
| Pulmonary endarterectomy | 11 (10.9) | NA | NA | NA | 11 (42.3) |
| *Conventional treatment* | | | | | |
| Conventional therapy only | 9 (8.9) | 0 (0.0) | 1 (9.1) | 0 (0.0) | 0 (0.0) |
| Conventional plus targeted therapy | 92 (91.1) | 18 (100.0) | 10 (90.9) | 20 (100.0) | 26 (100.0) |

Results are presented as absolute frequency (percentage).
IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable pulmonary arterial hypertension; CTD: connective tissue disease; CHD: congenital heart disease; CTEPH: chronic thromboembolic pulmonary hypertension; PDE-5I: phosphodiesterase-5 inhibitors; ERA: endothelin-1 receptor antagonists; NA: not applicable.

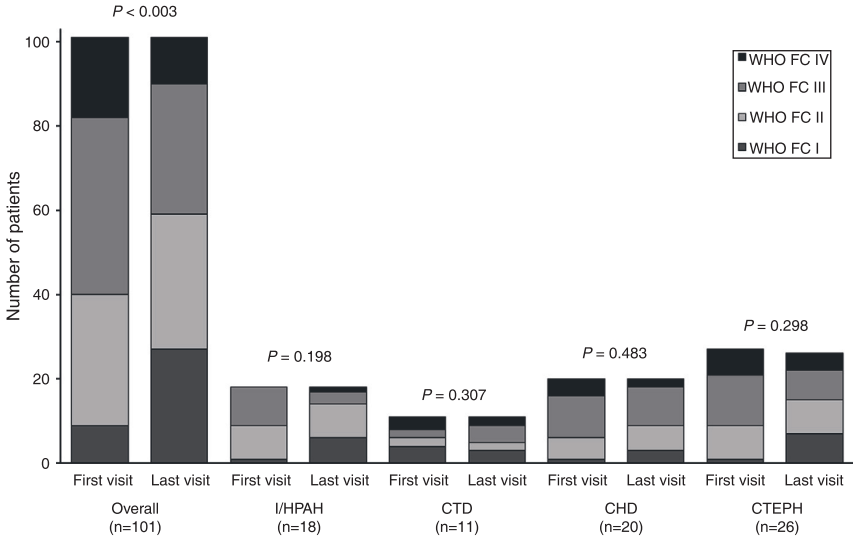


**Figure 2** Change in functional capacity, measured by WHO FC, from first do last visit.

under combination therapy, and dual therapy was the most frequent type of treatment (36.4% and 45.0%, respectively). Patients with non-operable CTEPH or with residual persistent PH were mostly under monotherapy (57.7%), particularly with ERAs (46.2%).

During patient follow-up, functional capacity improved significantly ($P$ < 0.003) from first to last visit for the overall study population, as illustrated in Fig. 2. Mean 6MWD significantly improved in the overall population ($P$ = 0.003) and in the subgroup of I/HPAH patients ($P$ = 0.011). CHD subgroup was the only one to show a significant ($P$ = 0.040) improvement in NT-proBNP levels (Table 3).

There was a significant reduction in mPAP in the overall population ($P$ = 0.002) and in the subgroup of I/HPAH patients ($P$ = 0.008). PVR significantly improved in the overall population ($P$ = 0.008) and in the subgroup of I/HPAH patients ($P$ = 0.008). No significant changes were observed in RAP and CI for either the overall population or subgroup analyses.

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**Table 3** 6MWD and NT-proBNP evolution from first to last visit.

| | Overall ($n=101$) | | | | I/HPAH ($n=18$) | | | | CTD ($n=11$) | | | | CHD ($n=20$) | | | | CTEPH ($n=26$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First visit | | Last visit | | First visit | | Last visit | | First visit | | Last visit | | First visit | | Last visit | | First visit | | Last visit | |
| 6MWD, m | 319.6 | 132.9 | 357.7 | 162.1** | 360.7 | 117.5 | 463.3 | 163.1 | 297.3 | 53.6 | 282.5 | 163.8 | 330.7 | 24.1 | 319.8 | 164.8 | 289.4 | 144 | 337.2 | 156.2 |
| NT-proBNP, pg/mL | 1533.4 | 1758.3 | 1963.9 | 3627.2 | 1543.8 | 1712.5 | 1583.2 | 3761.9 | 2081.9 | 909.8 | 3392.8 | 3732.1 | 1139.3 | 277.4 | 1815.9 | 3671.7* | 2163.8 | 1805.5 | 2960.1 | 5098.3 |

Results are presented as mean SD.
6MWD: 6-min walk distance; NT-proBNP: N-terminal pro brain natriuretic peptide.
* <0.05.
** <0.01.

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**Table 4** Kaplan–Meier survival estimates.

| | Cumulative probability of survival, % |
|---|---|
| *Total cohort (n = 101)* | |
| 1 year from diagnosis | 86.6 |
| 3 years from diagnosis | 76.7 |
| 5 years from diagnosis | 64.1 |
| *Group 1 PH – PAH (n = 55)* | |
| 1 year from diagnosis | 91.8 |
| 3 years from diagnosis | 80.3 |
| 5 years from diagnosis | 66.2 |
| *Group 4 PH – CTEPH (n = 26)* | |
| 1 year from diagnosis | 81.5 |
| 3 years from diagnosis | 75.3 |
| 5 years from diagnosis | 67.3 |

PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension. Survival estimates for subgroups of PH were not calculated due to limitations introduced by reduced sample size and variable follow-up times in the subgroups.

## Survival

During the follow-up period, a total of 28 (27.7%) patients died of PH-related causes; 10.7% of deaths occurred in patients with I/HPAH, 25.0% with CTEPH, 10.7% with CTD, and 25.0% with CHD. Patients with WHO FC III or IV at baseline represented 67.9% of deaths. Median survival time from diagnosis by RHC for the 28 deaths was 3.1 years. At the time of death 35.7% of patients were under monotherapy, 39.3% under dual therapy, 17.9% under triple therapy, and only 2 patients (7.1%) were under exclusive conventional therapy.

Table 4 presents survival estimates for the overall study cohort and specific PH aetiologies. For the overall study cohort, 1-, 3-, and 5-year survival was estimated at 86.6%, 76.7%, and 64.1%, respectively. Fig. 3 shows the Kaplan–Meier survival curve for the overall cohort and

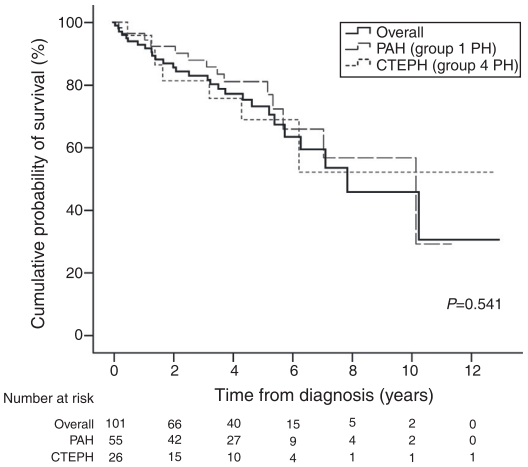


**Figure 3** Kaplan–Meier survival curve for the overall study cohort, patients with PAH (Group 1 PH) and patients with CTEPH (Group 4 PH).

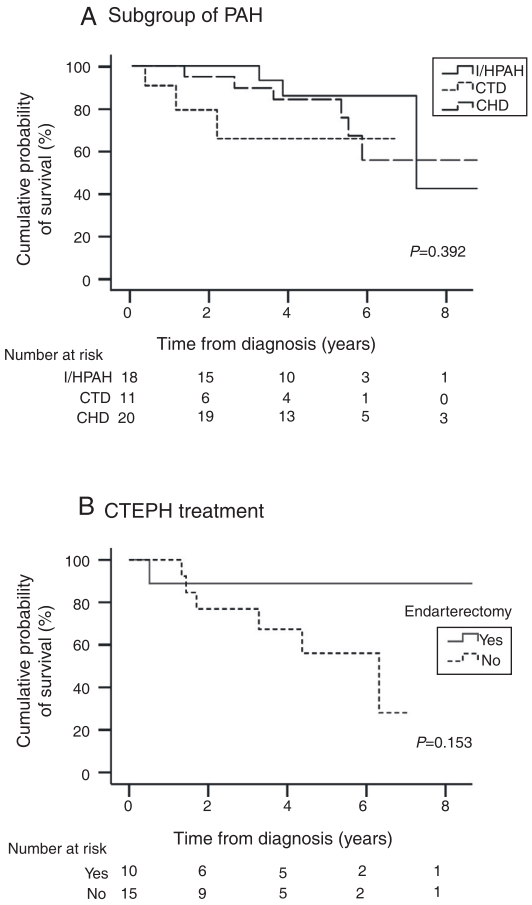


**Figure 4** Kaplan–Meier survival curves for subgroups of patients, according to (A) subgroup of PAH and (B) CTEPH treatment.

for patients with PAH vs. CTEPH. Fig. 4 shows specific Kaplan–Meier survival curves for subgroups of PAH (A) and according to CTEPH treatment (B).

Survival was significantly better for those 40 years old (10.5 vs. 6.4 years; $P = 0.003$) and in women with I/HPAH compared with men (9.3 vs. 4.5 years; $P = 0.039$); no other significant differences in survival were observed for gender, age, PH aetiology, and functional capacity analyses for the overall population and subgroups of aetiologies.

## Discussion

This study provides long-term data for patient phenotypes, clinical evolution, and survival in PAH and CTEPH of a Portuguese PH population. These results build on previous findings[21,24] and together they characterise the impact of this life-threatening disease in Portugal. The present study enrolled only patients with pcPH due to the substantially different disease characteristics and treatment approaches that could bias the results and ultimately hinder comparisons with other cohorts published over the years. Unlike previous studies, here we included patients with all types of PH, except for left heart disease, to provide a more

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accurate picture of pcPH as a whole. Left heart disease was the only PH group excluded from the analysis.

The PH dedicated software developed by the centre allowed the implementation of a mandatory case report form (CRF) with automatic alerts to avoid missing data in our clinical records. This methodology allowed us to build a true real-world cohort of PH patients from our region and following the most recent Nice recommendations.[25] This is particularly relevant because PAHTool® is currently licenced for implementation in several PH centres worldwide, and its widespread use is envisioned to allow the generation of relevant real-world data, which is badly needed in the context of this non-frequent condition but rapidly evolving field.

According to existing registries, some aetiologies are underrepresented in our cohort (particularly drugs and toxins induced PH, HIV and portal hypertension associated PH), which is most likely due to low physician awareness about PH.[21,26–36] CHD (36.3% of PAH group) contributed with a comparatively higher proportion of cases, which can be explained by the past low levels of detection and correction of heart defects in infancy in our country and by the fact that our centre was for a long time the only one to provide targeted therapy for PAH in the region. CTEPH was the most frequent aetiology after PAH, confirming the high prevalence of this frequently forgotten condition and in line with studies that included this subgroup of patients.[21,34,37–39]

Comparing our data with the most important registries in the field, we found that CTEPH age at diagnosis in our population is consistent with these registries[38–40]; although the mean age at diagnosis for our overall population is similar to the majority of PAH registries[26,29,32] the mean age for I/HPAH is clearly lower and near the pioneer registries[35,41] and those coming from the developing world,[42,43] but still in line with national data.[21] Female gender (66%) predominance is also in line with the majority of PH registries and cohorts.[21,26–35]

Baseline clinical characteristics at presentation indicate some delay in diagnosis, with most patients presenting with intermediate or high risk of mortality indicated by high NYHA FC, low 6MWD and high NT-proBNP according to risk assessment guidelines[3]; increased RAP (11.1 5.3 mmHg) and PVR (8.1 4.8 WU) are also consistent with these findings. The proportion of patients presenting with intermediate or high risk explains why the great majority of patients were treated with combination therapy: I/HPAH (88.9%), CTD (54.5%) and CHD (55.0%). These findings are, however, above what has been reported in recent European studies, as well as national data.[21,30,32,34,44] There is a particularly high proportion of I/HPAH (61.1%) patients under triple therapy, which is probably the result of the close follow-up adopted and continuous risk evaluation with early step up of the therapy. ERAs and PDE-5I were the most widely used drugs, which is in accordance with previous reports.[21,30,32,34,44] Still, they were used far more frequently in combination than what has been reported, which is in line with the most recent recommendations for the early use of sequential or upfront double combination therapy.[3,45]

Although pulmonary endarterectomy surgery is not routinely available in our country, patients are fully reimbursed by the Portuguese Public National Health Service if surgery is performed abroad. Despite limitations associated with the need for a cross-border, high risk procedure, 42% of CTEPH patients had the operation in a foreign centre, thanks to a protocol for surgical treatment of PH established in 2000. Non-operable patients, patients refusing pulmonary endarterectomy, or patients with residual persistent PH after pulmonary endarterectomy were predominantly treated with monotherapy (57.7%) and specially with ERAs (46.2%), as per previous studies.[39,40]

In terms of clinical outcomes during the period of the study, WHO FC, 6MWD, mPAP and PVR significantly improved for the overall population, which is in line with the accumulating evidence of substantial gains in long-term prognosis obtained over recent decades, following the introduction of several therapeutic alternatives.[3,30,32,34]

Although usual bias for survival estimates were eliminated in this study (including mixed population of incident/prevalent cases and ''immortal'' bias), survival estimates should still be considered with caution since there were substantial changes in treatment strategies during the course of the study. Nonetheless, survival estimates found for the total cohort and PAH follow the trends of the most relevant international registries[26–28,30,32,35]; the 1-year survival among CTEPH patients (81.5%) was considerably below estimates from other studies (88–97%),[37–40] which could be connected to difficulties of access to PEA surgery.

This study had several limitations. First, its single-centre nature might affect the representativeness of the findings for the overall Portuguese population, however, the study was conducted at one of the largest PH centres in the country, serving the northern region, with an ample and diverse group of patients currently being followed. Second, the relatively small sample size impaired the ability to perform more in-depth statistical analysis such as predictors of survival, however, in the context of a non-frequent disease the data provided by this study gives highly relevant insight to inform clinical practice. Third, the enrolment period for this study was long, which is associated with highly variable follow-up times and variable treatment approaches over time. Still, the low incidence of PH and the country/region dimension make enrolment over reduced periods difficult.

## Conclusions

This study provides long-term, real-world data for the management of PH in Portugal. It also demonstrates the potential of a dedicated information system for PAH in generating high-quality real-world data aimed at characterising PH in present clinical practice conditions. Patients presented mostly with intermediate or high risk of mortality which might be indicative of delay in diagnosis and highlights the need to increase awareness and early referral to expert centres for this condition among clinicians.

## Conflicts of interest

Abílio Reis is co-proprietary of the dedicated pulmonary hypertension software PAHTool®. The remaining authors have no conflicts of interests to disclose.

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## 3.3. Long-term Survival in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension: Insights from a Referral Centre in Portugal

***By Mário Santos, Ana Gomes, Célia Cruz, Joana Rocha, Miguel Ricardo, Fabienne Gonçalves, Luísa Carvalho, Margarida Vicente, Alzira Melo, and Abílio Reis.***

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ORIGINAL ARTICLE

# Long-term survival in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: Insights from a referral center in Portugal

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**KEYWORDS**
Pulmonary hypertension;
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Chronic thromboembolic pulmonary hypertension

**Abstract**
*Objectives:* This study aims to assess the long-term survival of pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) patients followed in a Portuguese pulmonary hypertension (PH) referral center.
*Methods:* We studied PAH and CTEPH patients diagnosed between January 2005 and December 2016. Cumulative survival was estimated using the Kaplan-Meier method. Survival trends were compared over two periods (2005-2010 vs. 2011-2016).
*Results:* Of the 142 studied PH patients (age 54±18 years; 31% male), 47 had CTEPH and 95 had group 1 PH. Most patients with CTEPH and idiopathic/heritable PAH (I/HPAH) were in NYHA III-IV at diagnosis (64% and 57%, respectively). At the time of death, 31% of patients with connective tissue disease (CTD)-associated PAH (CTD-PAH) and all I/HPAH patients were on double or triple combination therapy. No patient underwent lung transplantation. Pulmonary endarterectomy or angioplasty were performed in 36% of CTEPH patients. Age at diagnosis tended to increase over time in CTD-PAH (53±15 vs. 63±15 years; p=0.13) and I/HPAH (39±15 vs. 51±19 years; p=0.10). The five-year survival estimates for I/HPAH, CTD-PAH and CTEPH patients were 80%, 52%, and 81%, respectively. Over time, CTD-PAH and CTEPH showed better five-year survival (33 vs. 67% and 77 vs. 84%), but I/HPAH did not (84 vs. 75%).

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*Conclusions:* Our data indicate a trend toward improved survival over time of CTD-PAH and CTEPH patients treated at a Portuguese referral PH center. Earlier diagnosis, increasing use of parenteral prostanoids, and surgical treatment may further improve PH prognosis.


**PALAVRAS-CHAVE**
Hipertensão pulmonar;
Hipertensão arterial pulmonar;
Sobrevivência;
Hipertensão pulmonar tromboembólica crónica

**Sobrevivência a longo prazo na hipertensão arterial pulmonar e na hipertensão pulmonar tromboembólica crónica: dados de um centro de tratamento em Portugal**

**Resumo**
*Introdução:* Este estudo tem como objetivo avaliar a sobrevivência a longo prazo em doentes com hipertensão arterial pulmonar (PAH) e hipertensão pulmonar tromboembólica crónica (CTEPH) seguidos num centro de tratamento.
*Métodos:* Doentes diagnosticados com PAH ou CTEPH entre janeiro 2005 e dezembro 2016 foram incluídos. A sobrevivência cumulativa foi estimada utilizando o método Kaplan-Meier. Compararam-se os padrões de sobrevivência de dois períodos (2005-2010 *versus* 2011-2016).
*Resultados:* Foram estudados 142 doentes (54 ± 18 anos; 31% homens), 47 diagnosticados com CTEPH e 95 com PAH. A maioria dos doentes com CTEPH e etiologia idiopática/hereditária (I/HPAH) apresentava classe funcional NYHA III-IV ao diagnóstico (64% e 57%, respetivamente). Aquando da morte, 31% dos doentes com doença do tecido conjuntivo (CTD) e todos os doentes com H/IPAH recebiam terapia dupla ou tripla. Nenhum doente realizou transplante pulmonar. Endarterectomia pulmonar (PEA) ou angioplastia foram realizadas em 36% dos doentes com CTEPH. A idade de diagnóstico de H/IPAH (39 ± 15 *versus* 51 ± 19 anos; p = 0,10) e CTD (53 ± 15 *versus* 63 ± 15 anos; p = 0.13) tendeu a aumentar. A sobrevivência a cinco anos foi estimada em 80%, 52% e 81% para H/IPAH, CTD e CTEPH, respetivamente. No 2.º período, a sobrevivência a cinco anos melhorou nos doentes com CTD e CTEPH (33% *versus* 67% e 77% *versus* 84%), mas não nos I/HPAH (84% *versus* 75%).
*Conclusões:* Existe uma tendência de melhoria na sobrevivência de doentes com CTD-PAH e CTEPH tratados num centro de referência português. O diagnóstico precoce, o uso de prostanoides parenterais e a disponibilização de tratamentos cirúrgicos poderão traduzir-se em ganhos adicionais de sobrevida.


## Introduction

Pulmonary hypertension (PH) is characterized by an increase in pulmonary artery pressure. It can be associated with a wide range of conditions,[1] the most common of which are left heart disease and lung disease, in which PH has considerable prognostic significance but no indication for specific therapy.[2] The distinction between these causes and less frequent causes of PH such as pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) is often challenging and always critical, since the latter have an ominous prognosis without specific treatment.[3,4] Ten specific pulmonary vasodilators are currently available for PAH and there is robust evidence on the clinical benefits of pulmonary endarterectomy (PEA) for CTEPH patients.[2]

Despite notable advances in recent decades, rare diseases such as PAH and CTEPH still present numerous challenges. Early diagnosis is fundamental but still an unmet need. The more advanced the functional class at diagnosis, the worse the prognosis.[5,6] Regarding treatment, generalization of data from clinical trials is not straightforward, as these trials' study populations often differ from real-world patients.[7] Observational data from registries and cohort studies are accordingly crucial to provide insights on epidemiology, adherence to guidelines, effectiveness of treatments, and outcomes in clinical practice. Several international registries and PH referral center cohort studies have been published.[8] However, available data on PAH and CTEPH patients followed in Portugal are limited, especially in terms of long-term mortality.[9–11]

We studied PAH and CTEPH patients followed in a Portuguese PH referral center with the following aims: (1) to describe patients' clinical, functional and hemodynamic profile at diagnosis; (2) to characterize the use of specific pulmonary vasodilator treatments; and (3) to examine long-term mortality and survival trends between different time periods.

## Methods

This retrospective single-center study included all group 1 and group 4 PH patients followed in the Pulmonary Vascular Disease Unit of Hospital de Santo António, Centro Hospitalar do Porto (Porto, Portugal) between January 2005 and December 2016. This unit is the official referral center for the treatment of PH in the Northern region of the country, covering an adult population of 3.8 million. Demographic, clinical, hemodynamic, and treatment data were collected using dedicated PH software (PAHTool®, Inovultus Lda., Santa Maria da Feira, Portugal). Specific vasodilator treatments were collected from the last follow-up observation. All patients had incident PAH confirmed by right heart catheterization (RHC) using the criteria and PH classification from current international clinical guidelines.[2] The ethics committee of Hospital de Santo António authorized the study and waived patients' consent. Survival status (all-cause mortality) was assessed by chart review through February 1, 2017.

Demographic and clinical variables were summarized with descriptive statistics. Categorical variables were summarized as absolute frequency and percentage, and continuous variables were summarized as mean and standard deviation. Bivariate analysis was conducted using the Student's t test, Wilcoxon's test, Fisher's exact test, or chi-square tests, as appropriate. Cumulative survival was estimated using the Kaplan-Meier method. Multivariate Cox proportional hazards regression models were used to assess the unadjusted and adjusted association of PH etiology and mortality. To describe survival trends over time, patients diagnosed in two different six-year periods (2005-2010 vs. 2011-2016) were compared. A 5% significance level was employed for all analyses. The statistical analysis was performed using Stata software, version 12.1 (StataCorp LP, College Station, TX, USA).

## Results

### Overall population

We studied 47 group 4 (CTEPH) and 95 group 1 PH (PAH) patients. The latter had the following etiologies: congenital heart disease (CHD; n=32), idiopathic/heritable (I/HPAH; n=25), connective tissue disease (CTD; n=28), human immunodeficiency virus infection (n=3) and portal hypertension (n=7). The clinical characteristics of the overall study population are described in Table 1. Most group 1 and 4 PH patients were women and were in an advanced functional class (New York Heart Association [NYHA] III or IV) at diagnosis (Figure 1). CTEPH patients were older and had higher N-terminal pro-brain natriuretic peptide (NT-proBNP) levels despite lower mean pulmonary artery pressures.

Fifty-three percent of PAH patients were on two or three vasodilators, while 21% of CTEPH patients were on combination therapy (Table 2). Thirty-six percent of CTEPH patients received non-pharmacological treatment, either endarterectomy (n=14) or angioplasty (n=3). Reasons for CTEPH patients not undergoing interventional therapy were patient refusal in 20 (43%) and considered inoperable or at

**Table 1** Clinical characteristics of the study population at diagnosis.

| | Overall (n=142) | PAH (n=95) | CTEPH (n=47) | p |
|---|---|---|---|---|
| *Age, years* | 54±18 | 49±18 | 64±14 | <0.001 |
| *Male, n (%)* | 44 (31) | 32 (34) | 12 (26) | 0.32 |
| *Diagnosis, n (%)* | | | | |
| I/HPAH | 25 (18) | 25 (26) | NA | |
| CTD | 28 (20) | 28 (29) | NA | |
| CHD | 32 (23) | 32 (34) | NA | |
| PoPH | 7 (5) | 7 (7) | NA | |
| HIV | 3 (2) | 3 (3) | NA | |
| *NYHA, n (%)* | | | | 0.41 |
| I/II | 52 (38) | 33 (36) | 19 (43) | |
| III/IV | 84 (62) | 59 (64) | 25 (57) | |
| 6MWT, m | 313±134 | 307±140 | 327±119 | 0.46 |
| NT-proBNP, pg/ml | 741 (253-2202) | 570 (207-2183) | 1071 (363-2657) | 0.04 |
| *Hemodynamics* | | | | |
| mPAP, mmHg | 51±16 | 53±18 | 45±7 | 0.03 |
| RAP, mmHg | 8±5 | 8±4 | 9±6 | 0.71 |
| CI, l/min/m$^2$ | 2.8±0.8 | 2.9±0.9 | 2.7±0.6 | 0.39 |
| PVR, WU | 9±5 | 9±5 | 8±3 | 0.52 |

6MWT: 6-min walk test; CHD: congenital heart disease; CI: cardiac index; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; HIV: pulmonary hypertension associated with human immunodeficiency virus infection; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; NA: not applicable; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association functional class; PAH: pulmonary arterial hypertension; PoPH: portopulmonary hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: Wood units. NT-proBNP levels are presented as median and interquartile range.

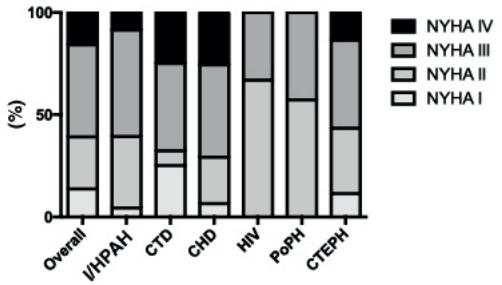



**Figure 1** Functional capacity measured by NYHA functional class at time of diagnosis of pulmonary hypertension patients according to etiology. CHD: congenital heart disease; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; HIV: pulmonary hypertension associated with HIV infection; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; NYHA: New York Heart Association functional class; PoPH: portopulmonary hypertension.

high operative risk in 10 (21%). None of the patients underwent lung transplantation.

## Clinical characteristics of patients over time

The clinical characteristics of patients diagnosed in the periods 2005-2010 and 2011-2016 are displayed in Table 3. Over time, age at diagnosis tended to increase in CTD-associated PAH (CTD-PAH) and I/HPAH patients and decreased significantly in CHD. At diagnosis, most patients with CTD and I/HPAH were in NYHA functional class III-IV, a scenario that did not improve over time. By contrast, CTEPH patients were predominantly in NYHA I-II at diagnosis in the more recent period (2011-2016). No significant hemodynamic differences at diagnosis were observed over time across the PH classification subgroups. In the I/HPAH subgroup, five (36%) patients diagnosed during the period 2005-2010 were positive on vasoreactivity testing, compared to only one (9%) during the period 2011-2016.

The trend toward higher percentages of triple combination therapy in the period 2005-2010 (Table 3) is related to the different follow-up time. At two-year follow-up, therapeutic aggressiveness in PAH patients was similar between periods (p=0.93), as 39% and 9% underwent double and triple combination therapy, respectively, in the 2005-2010 period, compared to 36% and 9% in the more recent period.

## Survival analysis

The mean follow-up period was 4.4±3.3 years. There were 49 (35%) deaths. The mean one-year, three-year and five-year survival of group 1 and group 4 PH patients are presented in Figure 2. CTD-PAH patients had the worst prognosis, with only 52% patients surviving five years after diagnosis (Figure 2). At the time of death, 31% of CTD-PAH and all I/HPAH patients were on double or triple vasodilator therapy, while 20% were under prostanoid therapy. CTEPH patients who did not undergo PEA showed worse prognosis after five years of follow-up, with 72% survival, compared to those who were surgically treated (94%). CTEPH patients treated with PEA were younger (55±11 vs. 67±15 years; p=0.09), presented with a lower 6-min walking distance at diagnosis (277±150 vs. 353±92 m; p=0.07) and had higher pulmonary vascular resistance (10±3 vs. 7±3 Wood units; p=0.03). No other relevant differences were found between these patients.

With regard to I/HPAH and CTD-PAH, while age (hazard ratio [HR] 1.08; 95% confidence interval [CI]: 1.04-1.16) and 6-min walking distance at diagnosis (HR 0.99; 95% CI: 0.99-0.99) were associated with prognosis, gender (HR 1.78; 95% CI: 0.70-4.53) and NYHA functional class (HR 2.06; 95% CI: 0.78-5.50) were not. Regarding CTEPH patients, in unadjusted analysis, PEA tended to be associated with lower mortality (HR 0.15; 95% CI: 0.02-1.22) but not after adjusting for age (HR 0.33; 95% CI: 0.04-2.97).

Figure 3 displays Kaplan-Meier curves and crude one-year, three-year and five-year survival estimates of I/HPAH, CTD-PAH and CTEPH patients diagnosed in the two different periods (2005-2010 and 2011-2016). The mean estimate of survival improved numerically over time in all etiologies, except for I/HPAH. The follow-up time (median and

**Table 2** Pulmonary hypertension treatment at last follow-up visit.

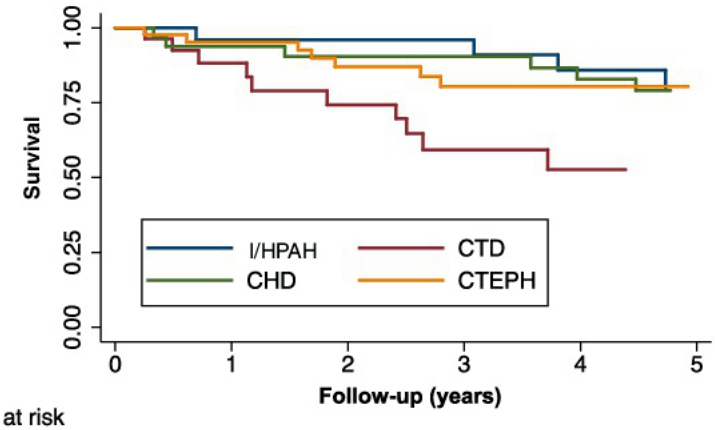
| | Overall (n=142) | PAH (n=95) | CTEPH (n=47) |
|---|---|---|---|
| *Pharmacological class, n (%)* | | | |
| CCB | 6 (4) | 6 (6) | 0 (0) |
| ERA | 105 (74) | 84 (88) | 21 (45) |
| PDE5i | 59 (42) | 51 (54) | 8 (17) |
| sGC | 13 (9) | 0 (0) | 13 (28) |
| Prostanoids | 20 (14) | 19 (20) | 1 (2) |
| *Combination therapy, n (%)* | | | |
| Single | 60 (42) | 38 (40) | 22 (47) |
| Double | 43 (30) | 34 (36) | 9 (19) |
| Triple | 17 (12) | 16 (17) | 1 (2) |
| *Non-pharmacological treatment, n (%)* | | | |
| PEA/pulmonary angioplasty | 17 (12) | 0 (0) | 17 (36) |

CCB: calcium channel blockers; CTEPH: chronic thromboembolic pulmonary hypertension; ERA: endothelin-1 receptor antagonists; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase-5 inhibitors; PEA: pulmonary endarterectomy; sGC: soluble guanylate cyclase.

**Table 3** Clinical characteristics of patients diagnosed in the two different periods.

| | I/H PAH | | | CTD-PAH | | | CHD PAH | | | CTEPH | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2005-2010 (n=14) | 2011-2016 (n=11) | p | 2005-2010 (n=9) | 2011-2016 (n=19) | p | 2005-2010 (n=15) | 2011-2016 (n=17) | p | 2005-2010 (n=13) | 2011-2016 (n=34) | p |
| *Age, years* | 39±15 | 51±19 | 0.10 | 53±15 | 63±15 | 0.13 | 52±16 | 34±13 | 0.001 | 63±12 | 65±15 | 0.70 |
| *Male, n (%)* | 5 (36) | 4 (36) | 0.83 | 0 (0) | 3 (16) | 0.21 | 5 (33) | 11 (65) | 0.26 | 2 (15) | 10 (29) | 0.32 |
| *NYHA, n (%)* | | 0.55 | | | 0.93 | | | 0.06 | | | 0.004 | |
| *I/II* | 6 (46) | 3 (30) | | 3 (33) | 6 (32) | | 2 (13) | 7 (44) | | 1 (8) | 18 (56) | |
| *III/IV* | 7 (54) | 7 (70) | | 6 (67) | 13 (68) | | 13 (87) | 9 (56) | | 11 (92) | 14 (44) | |
| *6MWT, m* | 344±130 | 260±155 | 0.18 | 331±155 | 242±152 | 0.20 | 348±124 | 294±134 | 0.29 | 284±139 | 349±103 | 0.13 |
| *NT-proBNP, pg/ml* | 983 (169-3027) | 801 (375-1489) | 0.69 | 269 (204-2813) | 1297 (313-2277) | 0.67 | 1415 (534-2815) | 253 (58-376) | 0.001 | 2468 (556-4922) | 1049 (329-1905) | 0.14 |
| *Hemodynamics* | | | | | | | | | | | | |
| mPAP, mmHg | 54±15 | 55±20 | 0.86 | 40±14 | 44±12 | 0.88 | 57±19 | 77±19 | 0.12 | 52±5 | 44±7 | 0.05 |
| RAP, mmHg | 10±5 | 11±6 | 0.51 | 6±3 | 6±2 | 0.91 | 8±4 | 6±3 | 0.32 | 9±4 | 9±6 | 0.81 |
| CI, l/min/m$^2$ | 2.8±0.5 | 2.9±0.9 | 0.88 | 2.6±0.3 | 3.1±0.8 | 0.41 | 2.4±1.6 | 2.8±1.0 | 0.73 | 3.0±1.1 | 2.7±0.6 | 0.51 |
| PVR, WU | 12±8 | 9±4 | 0.42 | 6±4 | 7±4 | 0.72 | 11±4 | 14±7 | 0.47 | 9±4 | 8±3 | 0.81 |
| Medical therapy[a] | | 0.12 | | | 0.29 | | | 0.52 | | | 0.34 | |
| CCB, n (%) | 5 (36) | 1 (9) | 0.12 | 0 | 0 | | 0 | 0 | | 0 | 0 | |
| Single, n (%) | 3 (21) | 3 (27) | | 7 (78) | 8 (42) | | 6 (40) | 6 (35) | | 7 (54) | 15 (44) | |
| Double, n (%) | 2 (14) | 5 (46) | | 1 (11) | 8 (42) | | 7 (47) | 8 (47) | | 4 (31) | 5 (15) | |
| Triple, n (%) | 7 (50) | 3 (27) | | 1 (11) | 2 (11) | | 2 (13) | 1 (6) | | 0 (0) | 1 (3) | |
| *Non-pharmacological treatment* | | | | | | | | | | | | |
| PEA/pulmonary angioplasty | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | | 0 (0) | 0 (0) | | 5 (39) | 12 (35) | 0.84 |

[a] Single, double and triple refer to specific pulmonary vasodilators (phosphodiesterase-5 inhibitors, endothelin-1 receptor antagonists, soluble guanylate cyclase and prostanoids).
6MWT: 6-min walk test; CCB: calcium channel blockers; CHD: congenital heart disease; CI: cardiac index; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association functional class; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; RAP: right atrial pressure; WU: Wood units. NT-proBNP levels are presented as median and interquartile range.




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| I/HPAH | 25 | 22 | 21 | 19 | 17 | 13 |
| CTD | 28 | 19 | 16 | 9 | 8 | 6 |
| CHD | 32 | 29 | 27 | 24 | 22 | 20 |
| CTEPH | 47 | 38 | 29 | 22 | 16 | 12 |

Survival estimates

| | 1-year survival | 3-year survival | 5-year survival |
|---|---|---|---|
| Group 1 PH | 90 [82-95] | 80 [70-87] | 70 [58-79] |
| I/H PAH | 96 [74-99] | 96 [74-99] | 80 [55-92] |
| CHD | 94 [77-98] | 90 [73-97] | 79 [59-90] |
| CTD | 88 [67-96] | 58 [35-76] | 52 [28-71] |
| CTEPH | 95 [83-99] | 81 [63-91] | 81 [63-91] |
| PEA angioplasty | | | |
| Yes | 94 [63-99] | 94 [63-99] | 94 [63-99] |
| No | 96 [77-99] | 72 [47-86] | 72 [47-86] |

Data presented as percentage [confidence interval].

**Figure 2** Survival curves of pulmonary hypertension patients according to etiology. CHD: congenital heart disease; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; PAH: pulmonary arterial hypertension; PEA: pulmonary endarterectomy; PH: pulmonary hypertension.

interquartile range) for patients included in 2005-2010 and 2011-2016 were 6.9 (3.7-9.5) years and 2.8 (1.2-4.8) years, respectively. The annual incidence rates in these periods were 9.3 (6.6-13.2) and 6.1 (3.8-9.7) per 100 person/years, respectively. Kaplan-Meier curves are shown in Figure 3.

## Discussion

These long-term data of PH patients followed at a Portuguese referral center illustrate the following: (1) at diagnosis most of patients were in an advanced NYHA functional class; (2) the mean age at diagnosis of I/HPAH patients is increasing over time; (3) specific treatments and survival are comparable to other registries and cohort studies; and (4) PEA and lung transplantation are underused treatments despite being associated with better survival of CTEPH and PAH patients.

Most patients, 64% of group 1 PH and 57% of CTEPH, presented in NYHA functional class III-IV at diagnosis. Over time, a reduction was observed in the proportion of patients with advanced functional incapacity only in the CTEPH subgroup (92 vs. 44%, p=0.004). Observational data from registries in the UK, France and the USA that enrolled a broad spectrum of PAH etiologies consistently showed that patients diagnosed in NYHA class I and II had lower mortality than those in NYHA class III and IV.[5,12,13] The earlier detection of CTEPH in our patients in the more recent study period might be explained by clinicians' and patients' increased awareness of this disease due to local and international campaigns.[14–16] Despite our continued efforts, more has to be done to diagnose patients earlier, particularly in group 1 PH, such as establishing screening programs in high-risk populations and raising awareness of the disease. Currently, PH care in Portugal is organized into four regional treatment centers to which patients with suspected PH should be sent for assessment. Further development of this referral network might help the early diagnosis of PH.

Changes in the demographic landscape of PAH have been consistently described by several contemporary registries.[17,18] Our data corroborate the higher mean age at diagnosis of PAH, a disease classically described as

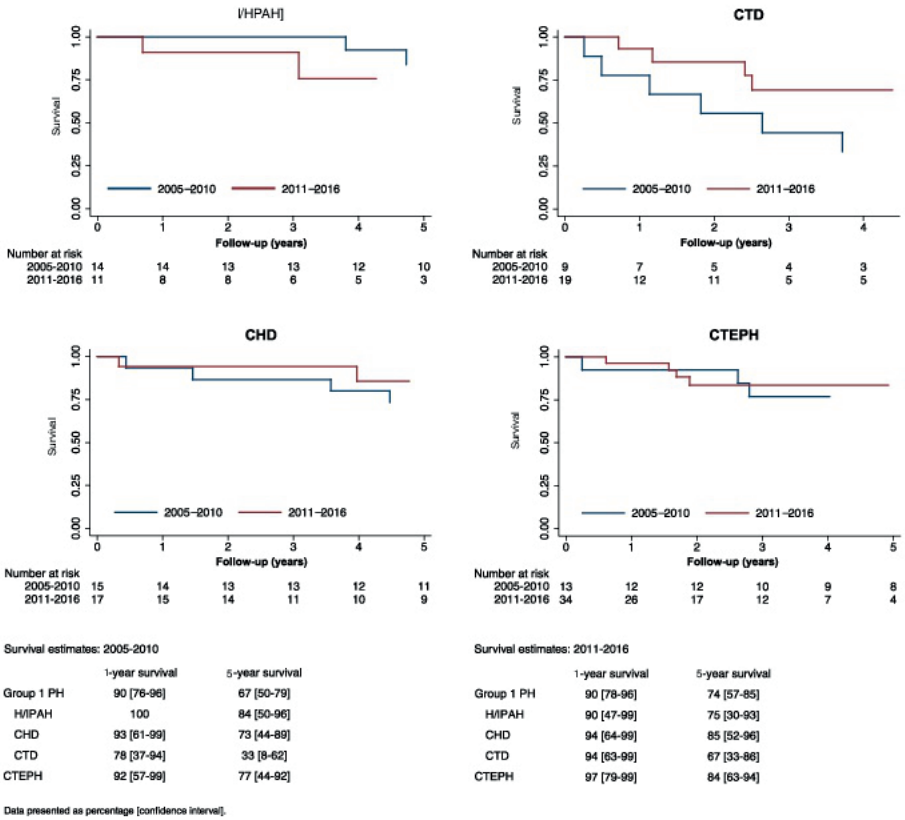



**Figure 3** Survival curves of idiopathic/heritable pulmonary arterial hypertension, connective tissue disease-associated pulmonary arterial hypertension, congenital heart disease-associated pulmonary hypertension and chronic thromboembolic pulmonary hypertension patients by time periods of diagnosis (2005-2010 and 2011-2016). CHD: congenital heart disease; CTD: connective tissue disease; CTEPH: chronic thromboembolic pulmonary hypertension; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; PH: pulmonary hypertension.

affecting young women. In addition, in our study age was independently associated with prognosis. This trend may reflect increased life expectancy, the widespread availability of screening tools like transthoracic echocardiography, and growing awareness regarding PAH in the medical community.[19] Irrespective of the underlying cause of this demographic shift in PAH patients, this subset of older patients poses specific clinical challenges regarding their response to pulmonary vasodilators and their potential side effects, which need to be addressed in future studies.

In line with previous studies,[5,20] the PH patients with the worst prognosis were those with CTD-PAH, who presented a five-year survival of 52%. Prognosis in this subset of patients showed improvement over time (Figure 2) despite the similar functional class at diagnosis in the two periods (NYHA III-IV class: 67 vs. 68%; p=0.93). We hypothesize that a more aggressive treatment approach can, at least in part, explain this better survival. In contrast, survival of patients with I/HPAH was unexpectedly worse in the more recent study period. Given the similar aggressiveness of vasodilator treatment in this subgroup over time, we speculate that the higher percentage of vasoreactive PAH patients (36% vs. 9%) can explain the worse survival. This difference may reflect survival bias, given the better prognosis of vasoreactive PAH. The overall survival rates of this subgroup (one-year and five-year survival rates of 95% and 80%, respectively) were similar to those of other registries,[21] including one recently published by another Portuguese referral center.[11]

At the time of death, only 20% of PAH patients were under parenteral prostanoid therapy. The underuse of parenteral prostanoids in severe PAH has been reported by others.[22–24] Physicians overlooking disease progression and underestimating its severity, organizational deficiencies in the management of this complex therapy, late referral, and patients' refusal may all contribute to the underuse of prostanoids in PAH.[25] Patient refusal, particularly by older patients, and social and cultural factors hindering self-management of continuous parenteral therapy were the main obstacles we found in our clinical practice. The lung transplantation numbers in our cohort reflect the constraints on this very effective treatment for PAH in Portugal, given the low volume of lung transplantations performed, particularly for PAH patients. This is a major issue that should be dealt with in the near future, by collaborating with national surgical centers or with foreign PH expert centers in the European Reference Network on respiratory diseases (ERN-LUNG) recently approved by the European Commission.[26]

As in previous reports from Portugal,[9,11] CHD-associated PAH represented a significant proportion of our cohort, which may be due to the limited access to corrective cardiac surgery in the past. Despite the lower age and better functional class at diagnosis, and a trend toward better survival

over time, efforts should be made to enhance the prevention of PH development by early referral of these patients to the recently designated congenital heart disease expert centers network.[27]

Estimated one-year and five-year survival in our CTEPH patients was 95% and 81%, respectively. These outcomes are in line with those reported in other registries (one-year: 88-97%; five-year: 65-83%).[9,28–31] PEA is the cornerstone treatment for CTEPH patients.[2] It is potentially curative and is associated with low in-hospital mortality if performed in high-volume centers.[32] Despite robust evidence of its benefits, underuse of PEA has been reported in previous registries. Escribano-Subías et al.[28] showed that this underuse is particularly marked in centers without PH expertise, in which only 5% of CTEPH patients underwent PEA, compared to 48% of those treated in expert centers. Almost 40% of our CTEPH patients underwent PEA or angioplasty after referral to a European high-volume surgical center. After adjusting for age, PEA was no longer associated with better survival, suggesting that some of the observed survival differences between operated and non-operated subgroups are accounted for by patient characteristics. The low statistical power, and consequent wide confidence intervals, should also be taken into consideration when analyzing these results. The main reason for not undergoing PEA was patient refusal to undergo the procedure in a foreign center, despite the existence of a national program that covers all expenses of cross-country care in this field. The majority of non-operated patients were treated with pulmonary vasodilators, initially with an endothelin receptor antagonist and later with a soluble guanylate cyclase stimulator, recently approved for the treatment of non-operable patients and those with persistent PH after PEA.[2]

Our study has several limitations that should be considered. The single-center nature of our data limits the generalizability of our conclusions, as etiologies and access to PH treatments may vary significantly across different centers. The small number of patients in some of the subgroups limits wider inferences. Despite the strong signs of improvements in survival, our analysis is underpowered to detect statistically significant time trends in the survival of patients diagnosed at different periods.

## Conclusions

Our data consistently indicate a trend toward improved survival over time of PH patients treated at a Portuguese referral PH center, except for I/HPAH. Efforts to achieve an early diagnosis, to increase use of parenteral prostanoids and to promote the delivery of surgical treatments to PH patients are needed to further improve their prognosis.

## Conflicts of interest

The authors have no conflicts of interest to declare.

## Acknowledgments

None.

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## 3.3.1. Lessons from pulmonary hypertension registries

***By Marc Humbert***

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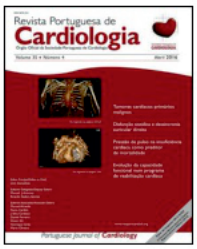

EDITORIAL COMMENT

# Lessons from pulmonary hypertension registries

## Lições retiradas dos registos de hipertensão pulmonar

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Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are major causes of pulmonary hypertension (PH) that have benefited from novel medical, interventional and surgical strategies in the last two decades.[1–3] Patient registries have provided important information on the clinical characteristics and natural history of different forms of PH.[4,5] Since the US National Institutes of Health (NIH) registry conducted in the 1980s, subsequent registries and databases have yielded additional information on the demographic factors, treatment, and survival of patients with different forms of PH, including PAH and CTEPH.[6–9] These registries have enabled comparisons between populations in different eras and environments.[10,11] In addition, the NIH and French registries have developed equations to predict one-, two- and three-year survival of patients with idiopathic, heritable, and drug-induced PAH.[12–15] These equations have been widely used as comparators in subsequent studies, in order to present indirect evidence of improved outcomes.[4] Since then, the US Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) has produced different tools, including the REVEAL score and the REVEAL score calculator, that can be used to predict one-year survival of PAH patients.[15,16] More recently, three large European registries have tested a risk assessment instrument derived from the 2015 European Society of Cardiology/European Respiratory Society PH guidelines[1,2] in large cohorts of PAH patients, underscoring the importance of well-designed multicenter registries to support clinical research in PH.[17–20]

An important observation of PAH and CTEPH registries is that survival in the modern treatment era has improved compared with that observed previously.[5,14,21] In addition, PAH registries consistently show that outcomes vary markedly between different PH etiologies, PAH complicating the course of connective tissue diseases being associated with worse outcomes than idiopathic PAH.[13,16,22] Continuing systematic clinical surveillance of PH is essential as treatment evolves.

In the current issue of the *Journal*, Santos et al. present original data on the long-term survival of PAH and CTEPH patients diagnosed between 2005 and 2016 in a Portuguese PH referral center (Hospital Santo António, Centro Hospitalar do Porto).[22] These data indicate that there is a trend for better outcomes in Portuguese PH patients treated in an expert center, but they also confirm that PAH and CTEPH remain disabling and life-limiting conditions.[22] The authors should be congratulated for their results, and also for developing dedicated PH software

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(PAHTool®, Inovultus Lda., Santa Maria da Feira, Portugal). This software is a major achievement of the Portuguese PH research community and is currently disseminated and used worldwide on a daily basis. For example, the PAHTool® is used in the 25 centers of the French Registry, and has been instrumental in the generation of recent data on PH risk assessment.[19]

Research and care for rare diseases is a timely topic in Europe, with the recent approval by the European Commission's Board of Member States of 24 European Reference Networks (ERN), including one for rare respiratory diseases (ERN-LUNG).[23] ERN-LUNG is currently made up of 60 centers in 12 countries and is organized into nine core networks representing the diversity of diseases and conditions affecting the respiratory system, including PH. In the PH Core Network, Portugal is represented by the Centro Hospitalar do Porto. Of note, ERN-LUNG has won the competition for a grant from the European Union for establishing registries within ERN-LUNG where they are still lacking, and for making existing registries, such as PH registries, fully interoperable.[24] ERN-LUNG has proposed building a comprehensive infrastructure for patient data management within ERN-LUNG, and PH will be a key condition tested in this registry warehouse.

In the past 20 years, major changes have taken place in the epidemiological and treatment landscape of PAH and CTEPH. Santos et al. have shown improvements in survival of PH patients in the modern management era in Portugal. The next challenge will be to further improve PH patient outcomes, resulting from better implementation of diagnosis and treatment guidelines and stronger support for basic, translational and clinical research at the national and international level.

## Conflicts of interest

The author has no conflicts of interest to declare.

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# 4. CHAPTER IV – Looking for a global PH patient's evaluation: health-related quality of life, disability, and overall quality of life

Besides the traditional clinical indicators used in clinical practice and research, it is increasingly important to assess the actual impact of disease and treatments on patients' lives. With such purpose, different measures of quality of life (QoL), health-related quality of life (HRQoL) and functionality/disability are available for use in clinical practice and research. Some outcome measures were developed for a specific disease context, while others are applicable to a broader population.

CAMPHOR is a patient-reported outcome measure (PROM) specifically developed to assess QoL impairment in PH patients. We conducted the study *"Portuguese Validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) Questionnaire",*[92] that was published in Health and Quality of Life Outcomes (2016). The Portuguese version showed good psychometric properties and was found to be valid and reliable, being therefore recommended for use. This was at the time the only disease-specific PROM validated for the Portuguese PH population.

Since PH is a highly debilitating condition with potentially relevant impact on quality of life, and there are numerous questionnaires to evaluate that impact, we conducted a study to assess the self-reported HRQoL of Portuguese PH patients using two questionnaires, one specifically designed for PH (CAMPHOR) and a general one (NHP). *"Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study",*[90] was published in BioMed Research International (2018). HRQoL showed to be impaired in Portuguese patients with PAH and other forms of pc-PH, particularly in patients with increased disease severity. Both general (Nottingham Health Profile, NHP) and disease-specific instruments (CAMPHOR) showed comparable HRQoL impairment in this patient population. CAMPHOR also showed a moderate impairment in overall QoL. WHO FC, 6MWD, and Borg dyspnea index were highly correlated with HRQoL impairment in this cohort, as well as with QoL measured through CAMPHOR. Despite some limitations, namely in measuring mental status, CAMPHOR demonstrated to be a useful disease-specific instrument and it was, at the time, the only instrument designed for PH measuring of overall QoL.

In addition to QoL, it is also of the upmost importance to assess the degree of disability that PH patients endure. Therefore, we conducted the study *"Disability and Its Clinical Correlates in Pulmonary Hypertension Measured Through the World Health Organization Disability Assessment Schedule II (WHODAS 2.0): a Prospective, Observational Study"***,** accepted for publication in Jornal Brasileiro de Pneumologia. This study intended to evaluate the degree of disability of pre-capillary PH patients using WHODAS, an internationally recognized instrument for this purpose. Patients showed mild disability, which could be associated with the low to intermediate disease severity of the cohort. Higher degree of disability was found in the domains of Mobility and Life activities. The main clinical correlates of disability in this population were WHO functional class, fatigue, and dyspnea. WHODAS 2.0 scores at baseline predicted 6MWD and WHO functional class over an 11-month follow-up period. This study was the first to assess disability in PH using WHODAS 2.0, allowing a basis for comparison with other disease stages, one of the main goals of this WHO questionnaire.

## 4.1. Portuguese validation of the Cambridge pulmonary hypertension outcome review (CAMPHOR) questionnaire

***By Abílio Reis, James Twiss, Margarida Vicente, Fabienne Gonçalves, Luísa Carvalho, José Meireles, Alzira Melo, Stephen P. McKenna, and Luís Almeida***

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Health and Quality of Life Outcomes

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# Portuguese validation of the Cambridge pulmonary hypertension outcome review (CAMPHOR) questionnaire

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## Abstract

**Background:** Patients with pulmonary arterial hypertension (PAH) and other forms of precapillary pulmonary hypertension (PH) have impaired quality of life (QoL). The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is a PH-specific patient-reported outcome measure that assesses symptoms, activity limitations and QoL. It was originally developed in UK-English. The main objective of this study was to create an adaptation of the CAMPHOR suitable for a Portuguese-speaking population.

**Methods:** A multi-step approach was followed: bilingual and lay panel translation; cognitive debriefing interviews; and psychometric testing in repeated postal surveys (2 weeks apart) including assessment of internal consistency, reproducibility and validity. The Nottingham Health Profile (NHP) questionnaire was used as a comparator instrument to test convergent validity.

**Results:** The CAMPHOR was translated without difficulty by the two panels. Cognitive debriefing interviews showed the questionnaire was easily understood and considered relevant to patients' experience with their illness. Psychometric evaluation was performed with 50 PAH patients (47 ± 14 years, 37 women). Cronbach's alpha coefficients showed good internal consistency for the three CAMPHOR scales [Symptoms = 0.95; Activities = 0.93 and QoL = 0.94]. Test-retest coefficients showed that all scales had excellent reliability (Symptoms = 0.94; Activities = 0.89 and QoL = 0.93), indicating low levels of random measurement error. The CAMPHOR correlated as expected with the NHP. The magnitude of correlations followed a similar pattern to those in the original development study. The CAMPHOR also exhibited evidence of known group validity in its ability to distinguish between self-reported severity and general health groups.

**Conclusions:** A valid and reliable version of the CAMPHOR questionnaire for the European Portuguese-speaking population was developed and is recommended for use.

**Keywords:** Pulmonary hypertension, Precapillary pulmonary hypertension, Pulmonary arterial hypertension, Quality of life, CAMPHOR, Portuguese adaptation, Nottingham Health Profile

## Background

Precapillary pulmonary hypertension (PH) is characterized by an obstructive vasculopathy of the pulmonary circulation leading to increased pulmonary arterial pressure, pulmonary vascular resistance and, eventually, right-sided heart failure and death [1–4]. Multiple conditions and comorbidities are associated with PH [5]. Patients present unspecific symptoms, such as exertion dyspnoea, fatigue, chest pain, palpitations, oedema or syncope, resulting in frequently delayed diagnosis [4].

PH prognosis improved in recent years due to better understanding of PH pathobiology, availability of new drugs (endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators and prostacyclin analogues) and renewed therapeutic strategies [6–9]. Still, a cure for pulmonary arterial hypertension (PAH) and other precapillary forms of PH is far from being available.

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The impact of the disease and some types of treatment, like parenteral drugs or oxygen administration, can lead to impaired QoL, social isolation, as well as anxiety and depression [10]. Assessments of health-related quality of life (HRQoL) are currently recommended during global evaluation of PH patients, both in the context of clinical trials and routine clinical practice. Although some generic questionnaires such as the Short Form 36 Health Survey (SF-36) have shown prognostic value in PAH [11, 12], generally the use of generic questionnaires or those specific to other conditions has important limitations if they are not eventually validated in an appropriate PH sample [13]. Several attempts to evaluate other generic questionnaires, such as Nottingham Health Profile (NHP), and EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) or other disease-specific questionnaires, such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ) or the Chronic Heart Failure questionnaire (CHQ), have failed to prove their specificity for the disease both in real life settings and clinical trials [14–21]. This lead to the development of disease-specific questionnaires such as the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [12, 13], and more recently, the emPHasis-10 [22] and the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT) [23], which are under evaluation. Disease-specific assessment instruments provide outcome measures that are more relevant to actual patient experience. Evidence also demonstrates that these outcomes are more sensitive to change than generic ones [24–29].

The CAMPHOR was originally developed and validated in the United Kingdom, [30] and subsequently adapted for use in the US, Canada, Australia/New Zealand, Sweden and Austria/Germany/Switzerland [13, 31–34]. It consists of three different scales: a 25-item Symptom scale, to assess energy, breathlessness and mood (low score indicates minimal symptoms); a 15-item Activity limitations scale with a 3-point rating system (score ranges from 0 to 30, lower score indicates minimal activity limitation); and a 25-item QoL scale (lower score indicates better QoL) [30].

This paper describes the Portuguese translation and validation of the CAMPHOR. The development of this language version will allow the use of CAMPHOR in routine clinical practice and in clinical trials in the European Portuguese-speaking population with PAH and other precapillary forms of PH.

## Methods

CAMPHOR translation and validation was based in three main stages: (1) bilingual and lay panel translation; (2) cognitive debriefing interviews; and (3) psychometric testing in repeated postal surveys, 2 weeks apart. Psychometric analyses included test-retest reliability, internal consistency, convergent validity, and known group validity. The study was approved by the Independent Ethics Committee of Centro Hospitalar do Porto and written informed consent was obtained from all participants before enrolment in the study.

Step 1: Translation

The bilingual panel involved a group of six participants who had Portuguese as their primary language and were fluent in Portuguese and English. Participants were excluded if they had medical training, were a professional translator or if they were familiar with PH. The Principal Investigator lead the panel discussion and a representative of the original measure development team attended the meeting, advising in situations of difficult decision-making by explaining the original concept of the items. Each scale item was discussed until agreement was reached.

The main goal of this panel was to provide the initial translation of the questionnaire. When translating the content, emphasis was placed on achieving conceptual equivalence rather than providing a literal translation. In situations where agreement could not be reached, the panel provided alternative translations for later consideration by the lay panel.

A separate lay translation panel consisted of a group of five monolingual Portuguese-speaking participants with an average education level. The Portuguese translation of the questionnaire developed by the bilingual panel was presented and discussed. Participants were asked to comment on the language in terms of comprehension and acceptability. The main goal of this panel was to ensure that the language used in the questionnaire was adequate for respondents with average educational level.

Step 2: Cognitive Debriefing Interviews

Face-to-face cognitive debriefing interviews were conducted with 10 patients in the PH outpatient clinic at Centro Hospitalar do Porto—Hospital Santo António (Table 1). The purpose of the interviews was to assess the relevance, acceptability, comprehensiveness and understandability of the questionnaire items. During the interviews, participants were asked to complete the questionnaire, comment on any aspect they thought had been omitted and answer some specific questions about the questionnaire.

Step 3: Validation

To validate the Portuguese version of the CAMPHOR, 50 patients with precapillary PH were recruited in the outpatient clinic at Centro Hospitalar do Porto—Hospital Santo António, between 14SEP2012 and 16SEP2013. Their mean disease duration was 57.06 (SD = 58.81) months. During a programmed visit, participants were informed about the study

**Table 1** Demographic and baseline characteristics of the study samples

| Parameter | Cognitive debriefing interview panel (*n* = 10) | Psychometric testing panel (*n* = 50) |
|---|---|---|
| Gender, *n* (%) | | |
| Male | 3 (30.0) | 13 (26.0) |
| Female | 7 (70.0) | 37 (74.0) |
| Age, years | | |
| Mean | 47.8 | 46.8 |
| Range | 23–70 | 20–75 |
| Marital Status, *n* (%) | | |
| Single | 3 (30.0) | 12 (24.0) |
| Married/living as married | 5 (50.0) | 35 (70.0) |
| Divorced/Separated | 2 (20.0) | 3 (6.0) |
| Employment Status, *n* (%) | | |
| Student | 0 (0.0) | 2 (4.0) |
| Full-time | 2 (20.0) | 16 (32.0) |
| Part-time | 1 (10.0) | 0 (0.0) |
| Unemployed | 1 (10.0) | 0 (0.0) |
| Retired | 5 (50.0) | 23 (46.0) |
| Long-term sick leave | 1 (10.0) | 0 (0.0) |
| Homemaker | 0 (0.0) | 9 (18.0) |
| PH aetiology, *n* (%) | | |
| Idiopathic/Heritable PAH | 3 (30.0) | 12 (24.0) |
| Connective Tissue Disorders | 1 (10.0) | 7 (14.0) |
| Human Immunodeficiency Virus | 0 (0.0) | 1 (2.0) |
| Porto-Pulmonary Hypertension | 0 (0.0) | 3 (6.0) |
| Congenital Heart Disease | 3 (30.0)) | 11 (22.0) |
| Interstitial Lung Disease | 0 (0.0) | 1 (2.0) |
| Chronic Thromboembolic Pulmonary Hypertension | 3 (30.0) | 12 (24.0) |
| PH with unclear multifactorial mechanisms | 0 (0.0) | 2 (4.0) |
| Mixed | 0 (0.0) | 1 (2.0) |

*Abbreviations*: *PH* pulmonary hypertension

methodology, signed an informed consent form and received packs containing written instructions, two samples of the CAMPHOR and NHP questionnaires (to be filled in at home, 2 weeks apart) and a pre-paid postal return envelope. All participants received unique identification numbers. Only returned completed surveys were considered for analysis.

Demographic (birth date, gender, marital and working status) and clinical data (PH aetiology, WHO/NYHA functional class, 6MWD, NT-proBNP, treatment) were gathered from the PH clinic dedicated informatics system (PAHTool®, Inovultus Lda, Portugal) and exported to Microsoft Excel.

### Statistical analysis

The distributional properties of the measures were explored through descriptive statistics [mean, standard deviation, median and interquartile range (IQR) and floor and ceiling effects (% of patients scoring the minimum and maximum scores)]. Scores were compared by age and gender.

Internal consistency was assessed using Cronbach's alpha coefficients. Alpha measures the extent to which the items in a scale are inter-related. A low alpha (below 0.7) indicates that the items do not work together to form a scale [25]. In addition, item total correlations (ITCs) should be between 0.2 and 0.8.

The test-retest reliability of a measure is an estimate of its reproducibility over time when no change in the condition has taken place. It is calculated by correlating scores obtained on two different occasions. Spearman's rank correlation coefficient was used for the analyses. For low random measurement error, a correlation coefficient of ≥0.85 is necessary (26).

Convergent validity is used to determine the level of association between scores on one scale and those on a comparator scale that measures the same or related constructs. For the present investigation, the NHP was used as a comparator instrument. Portuguese CAMPHOR scores were correlated with NHP scores by Spearman rank correlation coefficients.

Known group validity can be assessed by testing the ability of a measure to distinguish between groups of people that differ according to some known factor. The factors used for the present investigation were self-reported general health (poor, fair, good, very good) and severity of symptoms (mild, moderate and severe).

Non-parametric tests for independent samples (Mann-Whitney *U* Test for two groups or Kruskal-Wallis One-Way Analysis of Variance for three or more groups) were employed to test for differences in CAMPHOR scores between groups.

Statistical analyses were performed using IBM SPSS version 21.0.

## Results

### Translation

Equal numbers of men and women (3 males and 3 females) were included in the bilingual panel. The mean age of the participants was 37 years (range 21–52 years). Most of the translation process occurred with little discussion and disagreement between panel participants. The main challenge during the translation was the selection of words that would allow the items to be expressed colloquially.

The lay panel involved one male and four female participants with a mean age of 37 years (range 16–66 years). The panel reported that the language of the questionnaire

was generally good, objective, direct, and clear. However, panel members suggested some alternative wording to improve understanding. For example, item 1 of the Symptoms scale was changed because the Lay Panel thought that "without strengths" rather than "low strengths" would be easier to understand.

### Cognitive debriefing interviews

All CAMPHOR questionnaires were completed within a mean of 17 min (standard deviation 10.5 min). In general, patients understood the questionnaire and assessed it as being simple and easy to complete. Three elderly, rural, low literacy patients needed supplementary information to fully understand the instructions. All patients found that the questionnaire reflected their health condition and daily activities. The questionnaire's content was considered appropriate, relevant and comprehensive. No questionnaire items were identified as inappropriate or unacceptable.

### Validation

Fifty patients were recruited (Time 1) and 47 (94 %) completed and returned the questionnaires. Three subjects withdrew from the study, one was lost to follow up and two others were submitted to surgery between the surveys. The mean time between repeated post surveys was 14.2 days (median 14.0; $n = 47$). Main PH aetiologies are shown in Table 1.

### Sample demographics

Table 1 shows participants' characteristics and Table 2 presents disease information at Time 1.

**Table 2** Disease information of the Psychometric testing panel

| Parameter | Psychometric testing panel ($n = 50$) |
|---|---|
| Self-reported general health, *n* (%) | |
| Poor | 4 (8.3) |
| Fair | 2 (4.2) |
| Good | 11 (22.9) |
| Very Good | 31 (64.6) |
| Self-reported severity of disease, *n* (%) | |
| Mild | 6 (12.2) |
| Moderate | 24 (49.0) |
| Severe | 19 (38.8) |
| Flare up, *n* (%) | |
| No | 41 (83.7) |
| Yes | 8 (16.3) |
| Requirement of oxygen or aids, *n* (%) | |
| No | 28 (57.1) |
| Yes | 21 (42.9) |

### Questionnaire descriptive scores

Descriptive statistics at Time 1 and Time 2 are shown in Table 3.

Floor (>10 % of patients scoring minimum) effects were identified in the CAMPHOR QoL scale Time 1 and the CAMPHOR QoL and Symptoms scales at Time 2. However, this is likely to reflect the mild nature of a subgroup of the sample. A possible ceiling effect might have occurred, since 16.3 % of the patients reached the maximum score in the QoL scale at Time 1. These effects were observed in the NHP scales.

### Internal consistency and reproducibility

Cronbach's alpha coefficients results are summarized in Table 4. The scales of Portuguese CAMPHOR showed excellent internal consistency with scales ranging between (0.93 and 0.95). Inter-item total correlations for each item are shown in Additional file 1: Tables S1, S2, S3. Reproducibility was above the required 0.85 level for all three CAMPHOR scales: Symptoms = 0.94, Activity limitations = 0.89 and QoL = 0.93.

### Convergent reliability

Table 5 shows the correlation between CAMPHOR and NHP (six sections and NHP-D) scales at Time 1. High correlations were observed between CAMPHOR symptoms and Emotional reactions, Physical mobility and Energy showing the importance of these factors on PH symptomatology. As expected, CAMPHOR Activities correlated more strongly with Physical mobility. The QoL scale correlated more strongly with Energy, Emotional reactions, Physical mobility and Overall distress, indicating that multiple factors influence QoL in PH.

### Association of CAMPHOR scores with demographic factors

No significant differences in CAMPHOR scores were found between participants grouped by age (above versus below median age) or gender.

### Known group validity

Table 6 shows the results of the known groups analyses. Significant differences in ASQoL scores were observed between patients grouped by overall general health and perceived severity of disease.

## Discussion

Current guidelines recommend initial and follow-up disease severity and QoL assessments to support decisions regarding PH treatment [35]. Previous validation of the CAMPHOR questionnaire in other geographical and cultural contexts demonstrated its superior specificity for PH versus general questionnaires, such as NHP, SF-36 or LHFQ. Furthermore, the development of the

**Table 3** Questionnaire descriptive statistics for Time 1 and Time 2

| Parameter | *n* | Median (IQR) | Mean (SD) | Min–Max | % Max scoring | % Min scoring |
|---|---|---|---|---|---|---|
| Time 1 | | | | | | |
| *CAMPHOR* | | | | | | |
| Symptoms | 45 | 6.0 (3.0–15.5) | 9.4 (7.9) | 0.0–25.0 | 8.9 | 2.2 |
| Activities | 45 | 10.0 (6.0–16.0) | 11.2 (6.4) | 2.0–27.0 | 4.4 | 2.2 |
| QoL | 43 | 6.0 (1.0–14.0) | 8.1 (7.3) | 0.0–25.0 | 16.3 | 2.3 |
| *NHP* | | | | | | |
| Energy Scale | 47 | 0.0 (0.0–33.3) | 27.0 (37.2) | 0.0–100.0 | 57.4 | 14.9 |
| Pain Scale | 48 | 0.0 (0.0–37.5) | 20.3 (31.1) | 0.0–100.0 | 58.3 | 2.1 |
| Emotional Reactions | 48 | 22.2 (11.1–44.4) | 27.8 (24.8) | 0.0–88.9 | 22.9 | 2.1 |
| Sleep Scale | 47 | 20.0 (0.0–60.0) | 30.2 (34.6) | 0.0–100.0 | 44.7 | 8.5 |
| Social Isolation | 49 | 0.0 (0.0–20.0) | 13.9 (24.2) | 0.0–80.0 | 71.4 | 2.0 |
| Physical Mobility | 47 | 12.5 (0.0–50.0) | 26.3 (26.2) | 0.0–87.5 | 29.8 | 2.1 |
| NHP-D | 44 | 3.0 (1.0–10.3) | 5.4 (5.7) | 0.0–20.0 | 18.2 | 2.3 |
| Time 2 | | | | | | |
| *CAMPHOR* | | | | | | |
| Symptoms | 42 | 5.0 (1.8–16.3) | 8.3 (7.9) | 0.0–25.0 | 16.7 | 2.4 |
| Activities | 44 | 6.0 (4.0–12.0) | 9.2 (7.2) | 0.0–30.0 | 2.3 | 2.3 |
| QoL | 42 | 4.5 (0.8–13.0) | 7.2 (7.1) | 0.0–25.0 | 23.8 | 2.4 |
| *NHP* | | | | | | |
| Energy Scale | 45 | 0.0 (0.0–33.3) | 25.9 (37.5) | 0.0–100.0 | 60.0 | 15.6 |
| Pain Scale | 42 | 0.0 (0.0–33.3) | 18.5 (29.5) | 0.0–100.0 | 57.1 | 2.4 |
| Emotional Reactions | 42 | 16.7 (0.0–33.3) | 25.7 (28.8) | 0.0–100.0 | 26.2 | 4.8 |
| Sleep Scale | 45 | 20.0 (0.0–60.0) | 28.9 (34.8) | 0.0–100.0 | 44.4 | 11.1 |
| Social Isolation | 43 | 0.0 (0.0–40.0) | 15.3 (26.8) | 0.0–100.0 | 69.8 | 2.3 |
| Physical Mobility | 44 | 25.0 (0.0–46.9) | 26.4 (26.3) | 0.0–100.0 | 29.5 | 2.3 |
| NHP-D | 39 | 3.0 (0.0–8.0) | 5.3 (6.3) | 0.0–23.0 | 25.6 | 2.6 |

*Abbreviations*: *CAMPHOR* Cambridge Pulmonary Hypertension Outcome Review, *IRQ* inter-quartile range, *Max* Maximum, *Min* minimum, *QoL* quality of life, *NHP* Nottingham Health Profile

CAMPHOR utility index added the possibility of cost-utility analyses, which is particularly relevant for PH disease management [36].

Our study demonstrates that our European Portuguese version of CAMPHOR is a valid, internally consistent and reliable patient-reported outcome measure for the European Portuguese-speaking population with precapillary PH. This study was conducted exclusively in Portugal, therefore the

**Table 4** Cronbach's Alpha coefficients for Time 1 and Time 2

| Instruments | Reliability coefficient | |
|---|---|---|
| | Time 1 (*n* = 50) | Time 2 (*n* = 47) |
| *CAMPHOR* | | |
| Symptoms | 0.95 | 0.95 |
| Activities | 0.93 | 0.95 |
| QoL | 0.94 | 0.94 |

*Abbreviations*: *CAMPHOR* Cambridge Pulmonary Hypertension Outcome Review, *NHP* Nottingham Health Profile, *QoL* quality of Life

**Table 5** Correlation coefficients between CAMPHOR scales and NHP

| Parameters | Symptoms (*n* = 50) | Activities (*n* = 50) | QoL (*n* = 50) |
|---|---|---|---|
| *NHP* | | | |
| Energy Scale | 0.82[a] | 0.76[a] | 0.75[a] |
| Pain Scale | 0.66[a] | 0.67[a] | 0.56[a] |
| Emotional Reactions | 0.78[a] | 0.66[a] | 0.78[a] |
| Sleep Scale | 0.40[a] | 0.47[a] | 0.55[a] |
| Social Isolation | 0.52[a] | 0.40[a] | 0.61[a] |
| Physical Mobility | 0.83[a] | 0.84[a] | 0.77[a] |
| NHP-D | 0.80[a] | 0.72[a] | 0.82[a] |

*Abbreviations*: *CAMPHOR* Cambridge Pulmonary Hypertension Outcome Review, *NHP* Nottingham Health Profile, *QoL* quality of life
[a]Correlation is significant at the 0.01 level

**Table 6** Mean scores by known groups

| Known groups | Symptoms | | Activities | | QoL | |
|---|---|---|---|---|---|---|
| | *n* | Mean (SD) | *n* | Mean (SD) | *n* | Mean (SD) |
| *General Health* | | | | | | |
| Very Good/Good | 13 | 4.5 (4.6) | 11 | 6.3 (2.9) | 13 | 3.8 (5.3) |
| Fair/Poor | 31 | 11.4 (8.2) | 33 | 12.7 (6.6) | 29 | 10.0 (7.5) |
| *P-value* | – | <0.01 | – | <0.01 | – | <0.05 |
| *Self-reported severity of disease* | | | | | | |
| Mild/Moderate | 27 | 7.3 (7.1) | 27 | 9.3 (5.6) | 26 | 5.9 (6.3) |
| Severe/Very Severe | 18 | 12.6 (8.2) | 18 | 14.0 (6.7) | 17 | 11.5 (7.5) |
| *P-value* | – | <0.05 | – | <0.01 | – | <0.05 |

*Abbreviations*: *QoL* quality of life, *SD* standard deviation

use of our version in other Portuguese-speaking countries cannot be recommended, due to significant differences in culture, literacy and language (both in terms of semantics and vocabulary).

Most of the patients in the cognitive debriefing panels reported that the instrument was easy to complete and all patients reported that the questionnaire covered all important aspects of their experience with the disease. Three patients needed, nonetheless, additional information to fully understand the instructions during the cognitive debriefing interviews; these were older patients, from rural settings and with low literacy skills, and after additional clarifications, they finally were able to understand the instructions. In our study, patients took a mean of 17 min to complete the questionnaire, which is substantially longer than patients in the original instrument (10 min) [30] and more in line with data from the German translation (15 min) [34]. We hypothesise that this longer completion time could be associated with lower literacy and higher proportions of patients from rural contexts in our population, however, literacy was not evaluated in our sample hampering further clarification.

In this study, the proportion of patients reaching maximum scores in the CAMPHOR QoL scale was surprisingly high, particularly when compared to previous validation studies (16.3 % vs. 0.0–0.7 % in other studies [13, 30–34]), which could be suggestive of a substantial ceiling effect. These results, could potentially be explained by disease severity, comorbidities, oxygen use, or even literacy. However, the proportion of patients reaching maximum scores is actually similar (or even higher) in the NHP comparator scale, which could be indicative of a tendency to the extremes in this population rather than a substantial ceiling effect. Given the similar results observed in the NHP comparator scale we do not envision this possible ceiling effect as a major limitation to the clinical use of this European Portuguese translation of CAMPHOR.

We found significant relationships between the CAMPHOR scales and the relevant domains of the NHP and the magnitude of the correlations followed a similar pattern to those described in the original development study [30]. The CAMPHOR also showed evidence of known group validity in its ability to distinguish between groups of patients known to differ between self-ratings of disease severity and general health. The study showed that patients with precapillary PH experienced diminished QoL and increased symptoms and functional limitations. Results are consistent with the findings that patients with PH experience impairment in HRQoL [32, 33].

The major limitation of the present study is the small sample size, but given the low prevalence of precapillary PH related disease it can be considered an adequate sample for the purpose. Further studies to demonstrate CAMPHOR clinical validity, namely correlations with NYHA/WHO functional class, 6MWD and biomarkers, in the Portuguese population are being conducted.

## Conclusions

In conclusion, this study gave sufficient evidence that our adaptation of CAMPHOR is an effective and consistent tool in European Portuguese-speaking population with precapillary PH. Incorporating this questionnaire in future clinical trials and especially in clinical practice will improve our global clinical evaluation of the PH patient and will improve knowledge of the health impact of PH. Routine HRQoL evaluation at first presentation and regularly during follow-up can help to educate/familiarize the patient with these tools and help physicians make evidence-based decisions.

## Additional file

**Additional file 1:** Supplementary Table 1. Item reliability statistics for Symptoms scale. Supplementary Table 2. Item reliability statistics for Activities scale. Supplementary Table 3. Item reliability statistics for Quality of life (QoL) scale. (DOC 294 kb)

### Abbreviations

6MWD, 6-min waling distance; CAMPHOR, Cambridge Pulmonary Hypertension Outcome Review; HRQoL, health-related quality of life; IQR, interquartile range; ITC, item total correlation; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NHP, Nottingham Health Profile; NYHA/WHO, New York Heart Association/World Health Organisation; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; QoL, quality of life; SF-36, short form 36 health survey

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### Authors' contributions

AR and LA contributed to study design, language translation, data collection, statistical analysis and manuscript writing. JT and SM contributed to language translation, statistical analysis and critical revision of the manuscript. MV contributed to data collection, statistical analysis and critical revision of the manuscript. FB, LC, JM and AM contributed to data collection and critical revision of the manuscript. All authors read and approved the final manuscript.

**Competing interests**
The authors declare no conflict of interest.

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## 4.2. Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study

***By Abílio Reis, Mário Santos, Margarida Vicente, Inês Furtado, Célia Cruz, Alzira Melo, Luísa Carvalho, Fabienne Gonçalves, Pedro Sa-Couto, and Luís Almeida***

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*Research Article*

# Health-Related Quality of Life in Pulmonary Hypertension and Its Clinical Correlates: A Cross-Sectional Study

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*Background*. Health-related quality of life (HRQoL) impairment is common in pulmonary hypertension (PH), but its clinical predictors are not well established. This study aims to characterize the HRQoL of patients with pulmonary arterial hypertension (PAH) and other precapillary forms of PH (pcPH) and to explore its clinical correlates. *Materials and Methods*. A cross-sectional, observational study of patients with documented PAH and other forms of pcPH. Patients completed two patient-reported outcome measures (PROM): Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) and Nottingham Health Profile (NHP). Clinical characteristics were retrieved from electronic medical records. *Results*. Mean CAMPHOR and NHP scores for the study population were indicative of a moderate HRQoL impairment. Patients in World Health Organisation Functional Classes (WHO FC) III/IV showed significantly worse HRQoL. The main clinical correlates of HRQoL were WHO FC, 6-minute walking distance (6MWD), and Borg dyspnoea index. Overall quality of life (QoL), assessed through CAMPHOR's QoL domain, showed patterns comparable to HRQoL measured by both instruments. *Conclusions*. HRQoL, measured by two different PROMs, is impaired in Portuguese patients with PAH and other forms of pcPH, particularly in patients with increased disease severity. WHO FC, 6MWD, and Borg dyspnoea index are highly correlated with HRQoL and QoL.

## 1. Introduction

Pulmonary hypertension (PH) encompasses a vast group of chronic and progressive disorders characterized by an increase in pulmonary artery pressure, which can be associated with a variety of aetiologies [1]. If left untreated, PH can cause right ventricular failure and, ultimately, death [2–5]. In clinical practice, several severity and prognosis indicators are usually assessed during patient diagnostic workup and management, including the World Health Organisation functional class (WHO FC), 6-minute walking distance (6MWD), Borg Dyspnoea Index, and several laboratory biomarkers, which include invasive hemodynamic evaluation [6–9]. However, these indicators do not provide a direct estimation of the overall health status and quality of life (QoL). Therefore, in recent years, there has been an increasing interest in measuring both health-related quality of life (HRQoL) and QoL using general or specific-disease patient-reported outcome measures (PROMs) [10].

Defining the concepts of health status, HRQoL, and QoL is yet a matter of controversy among experts, which is well expressed in the medical literature [11]. This leads to the lack of a standardised terminology, which can introduce substantial interpretation issues. So, every scientific investigation

in this field should start by clarifying the criteria used to define such concepts and, at the same time, by characterizing the properties and capacities of the instruments used to evaluate the populations under study. For the purpose of this study, we define health status as the narrower of the three concepts, including all aspects of physical, mental, and social functioning that characterize an individual at a given time. HRQoL, on the other hand, evaluates the effects of the physical, mental, and social aspects—and particularly the effects of illness and treatment—on the individual's sense of well-being. QoL is the broader of the three concepts covering all aspects of life, including non-health-related aspects such as economic status and social participation, to characterize an individual's overall sense of well-being.

In populations with PH, both HRQoL and QoL have been assessed through various instruments over the years. Initially, general scales such as the Short-Form 36 (SF-36) or the Nottingham Health Profile (NHP) were the most widely used to assess HRQoL; these instruments did not, however, allow complete QoL evaluation. Recently, a PH-specific instrument, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) [12], was developed and validated for use in various regions, both in clinical practice and in clinical research settings [13]. CAMPHOR was the first PH-specific instrument to be developed and it provided substantial advantages over previously used instruments. It includes targeted evaluation of PH-specific symptomatology and activities that allows a better characterization of HRQoL in the PH population and includes an additional domain specifically aimed at assessing overall QoL. CAMPHOR was carefully developed and validated for use in PH populations with its content derived directly from patients and, thus, it was widely used over the past decade and is currently validated for use in several countries [12, 14–17]. More recently, other PROMs, like emPHasis-10 [18] and PAH-SYMPACT® [19], have also been developed to allow adequate collection of patient-reported information on health status, but without the capacity to actually evaluate QoL. Therefore, CAMPHOR continues to play and important role in PH, since it is the only PROM that integrates measures of QoL and provides an actual measure of patient value.

Given the nature of the physiological changes that characterize PH, this condition is expected to impact patient functionality, HRQoL, and QoL. Actually, several studies have identified HRQoL impairment in varied PH populations [20]. Although the relationships between patient's clinical characteristics and HRQoL impairment were not fully elucidated, some clinical factors seem to be highly associated with these outcomes, including WHO FC, 6MWD, symptoms (dyspnoea, fatigue, chest pain), drugs and administration route, and mental health (anxiety and depression) [2, 20–24]. Still, given the infrequent nature of precapillary forms of PH and the difficulties in studying these populations, there is still a need for further data on this field.

On the other hand, although we have a significant number of studies with various PROMs in these populations [20], there is yet a lack of scientific evidence about the value of the retrieved information and about the most efficient and easy to administer ones. This study aims to characterize the HRQoL of patients with pulmonary arterial hypertension (PAH) and other precapillary forms of PH (pcPH) assessed by a general instrument (NHP) and a disease-specific instrument (CAMPHOR), to evaluate HRQoL impairment and to explore the correlations between clinical characteristics and HRQoL measured through these PROMs and, ultimately, to give insights into the value of such questionnaires in the global evaluation of patients with these highly debilitating conditions.

## 2. Materials and Methods

*2.1. Study Design.* This is a cross-sectional, observational study of consecutive patients with documented PAH and other forms of pcPH (confirmed by right heart catheterisation) followed at a specialised PH unit at a tertiary care centre in Northern Portugal (Pulmonary Vascular Disease Unit, Medicine Department, Centro Hospitalar do Porto, Porto, Portugal). During the process of CAMPHOR validation for the Portuguese PH population, patients were asked to complete two questionnaires aimed at assessing their HRQoL (CAMPHOR and NHP) and to complete a basic questionnaire on their demographic and clinical characteristics. Disease-specific clinical measures, including haemodynamic ones, were retrieved from the hospital electronic medical records (EMR).

The study received favourable opinion from the Ethics Committee of Centro Hospitalar do Porto (Porto, Portugal). The study protocol and data collection instruments were submitted and approved by the Portuguese National Data Protection Commission. All patients provided their written informed consent prior to inclusion in the study.

*2.2. Patient Population.* Patients were eligible to participate in the study if they were ≥18 years old and were able and willing to give their informed consent. Patients were excluded if they were unable to complete the study questionnaires due to illiteracy or cognitive impairment or if their medical records revealed a medical condition or circumstance that could compromise their ability to comply with the study protocol.

*2.3. Data Collection and Instruments.* HRQoL data were collected by self-administering questionnaires during a scheduled routine clinical visit. Participants were asked to complete 3 questionnaires: (1) CHAMPOR, (2) NHP, and (3) a general demographic/clinical questionnaire, which evaluated age, gender, race, income, education level, and self-reported length of PH diagnosis. Clinical and laboratory data were retrieved from the database of the dedicated EMR software of the Unit (PAHTool®, Inovultus Ltd., Santa Maria da Feira, Portugal).

*2.4. Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR).* CAMPHOR was the first questionnaire specifically validated for PH patients, designed to assess symptoms, functioning, and QoL in clinical practice and in clinical trials [12].

CAMPHOR consists of (1) a 25-item overall symptoms scale, scored 0–25, with higher scores indicating the presence of more PH symptoms; (2) a 15-item functioning scale, scored 0–30, with lower scores indicating good functioning; and (3) a 25-item quality of life scale, scored 0–25, with higher scores indicating poor QoL [12]. The QoL subscale was developed using the needs-based model [25, 26]; that is, it is based on the premise that QoL is derived from the ability of the individual to satisfy his/her needs [12].

The symptom and quality of life scales have dichotomous response options ("true"/"not true" or "yes"/"no") while the functioning scale has three-point response options ("able to do on own without difficulty"/"able to do on own with difficulty"/"unable to do on own").

*2.5. Nottingham Health Profile (NHP).* NHP is a questionnaire that allows the assessment of the general health status of a given population, which can be used to assess HRQoL. NHP comprises 38 items, which fall into six sections: energy level (3 items), pain (8 items), emotional reactions (9 items), sleep disturbance (5 items), social isolation (5 items), and physical mobility (8 items) [27]. Individual items are scored 1 for a "yes" response and 0 for a "no" response. The total score for each section represents the summation of item scores expressed as a percentage. For each section, scores range from 0 to 100, with higher scores representing greater perceived distress (i.e., impaired health status) [27].

*2.6. Statistical Analysis.* Descriptive data are presented as mean ± SD or frequency (%). Bivariate analysis correlating demographic and clinical variables with CAMPHOR/NHP dimensions scores was conducted using Spearman's Rank correlation coefficient (between quantitative variables) and using point-biserial correlation (between quantitative variables and binary nominal variables). Multiple linear regression analysis was conducted only for the significant correlations to identify possible demographic/clinical predictors for both CAMPHOR and NHP scales. This technique was chosen due to the quantitative nature of the dependent variables. Significant variables were selected using a stepwise approach (stepping method criteria: entry, 0.05; removal, 0.10) and no estimation problems were found. A dummy variable technique was used to incorporate qualitative independent variables in the regression models. The assumption of residual's normality for the multiple regressions was verified visually by inspection of the PP plot.

Statistical analyses were conducted with SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA), and results were considered significant if $P < 0.05$.

## 3. Results

*3.1. Study Population Characteristics.* A total of 49 patients accepted to participate in the study and completed the study questionnaires ($N = 49$). Table 1 summarises the demographic and clinical characteristics of the study population. Mean ± SD age was 50.4 ± 13.7 years and most patients were female (75.5%). Mean disease duration was

Table 1: Demographic and clinical characteristics of the study population.

| Characteristics | PH patients ($n = 49$) |
|---|---|
| Age, years | 50.4 ± 13.7 |
| Gender, *n* (%) | |
| Female | 37 (75.5) |
| Male | 12 (24.5) |
| Marital status, *n* (%) | |
| Single | 11 (22.4) |
| Married/divorced/widowed | 38 (77.6) |
| Working status, *n* (%) | |
| Full-time | 15 (34.7) |
| Homemaker | 9 (18.4) |
| Retired | 23 (46.9) |
| Disease duration, months | 57.1 ± 58.8 |
| PH aetiology, *n* (%) | |
| PAH and others | 37 (75.5) |
| CTEPH | 12 (24.5) |
| Comorbidities, *n* (%) | |
| Yes | 28 (57.1) |
| No | 21 (42.9) |
| WHO Functional class, *n* (%) | |
| I/II | 34 (69.4) |
| III/IV | 15 (30.6) |
| 6MWD, meters | 428.0 ± 105.8 |
| Borg dyspnea | 2.2 ± 2.6 |
| HR_Bas, bpm | 78.2 ± 11.6 |
| HR_Max, bpm | 107.9 ± 19.1 |
| SBP, mmHg | 113.4 ± 17.7 |
| DBP, mmHg | 68.2 ± 13.6 |
| O2Sat_Bas, mmHg | 94.0 ± 3.4 |
| O2Sat_Min, mmHg | 80.5 ± 15.1 |
| NT-proBNP, pg/mL | 684.6 ± 908.4 |
| RAP, mmHg | 7.1 ± 4.6 |
| mPAP, mmHg | 44.8 ± 18.2 |
| PAOP, mmHg | 9.8 ± 4.1 |
| CI, L/min/m$^2$ | 3.1 ± 0.9 |
| PVR, Wood units | 7.0 ± 4.3 |
| Diuretics, *n* (%) | |
| Yes | 29 (59.2) |
| No | 20 (40.8) |
| Oral anticoagulants, *n* (%) | |
| Yes | 24 (49.0) |
| No | 25 (51.0) |
| Calcium channel blockers, *n* (%) | |
| Yes | 5 (10.2) |
| No | 44 (89.8) |

Table 1: Continued.

| Characteristics | PH patients ($n = 49$) |
|---|---|
| Oxygen therapy, *n* (%) | |
| Yes | 20 (40.9) |
| No | 29 (59.1) |
| PH specific therapy, *n* (%) | |
| Monotherapy | 23 (46.9) |
| Combination therapy | 20 (40.8) |
| No therapy* | 6 (12.2) |
| PH specific therapy route, *n* (%) | |
| Oral | 36 (73.5) |
| Parenteral | 7 (14.3) |

Data displayed as mean ± SD, except when otherwise indicated; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; Borg: Borg dyspnea score; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; DBP: diastolic blood pressure; HR_Bas: baseline heart rate; HR_Max: maximum heart rate; mPAP: mean pulmonary arterial pressure; PAH: pulmonary arterial hypertension; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; O2Sat_min: minimum oxygen saturation; O2Sat_bas: baseline oxygen saturation; SBP: systolic blood pressure. *No therapy: CTEPH patients waiting for surgical treatment ($n = 2$); Porto-pulmonary hypertension waiting for liver transplantation ($n = 1$). Low risk congenital heart disease ($n = 2$), and idiopathic PAH before specific therapeutic introduction ($n = 1$).

57.1 ± 58.8 months. One or more comorbidities were present in 57.1% of patients. The most common PH aetiologies were chronic thromboembolic pulmonary hypertension (CTEPH) (24.5%), congenital heart disease (22.4%), idiopathic/heritable (22.4%), connective tissue disease (14.3%), and others (16.3%). Others included PAH-associated portal hypertension and HIV (3 and 1 patients) and 4 patients with group 5 PH. To allow meaningful statistical analysis, PH aetiologies are, from this point on, categorised as PAH and others (including Group 1 PH and Group 5 PH) and CTEPH (Group 4 PH).

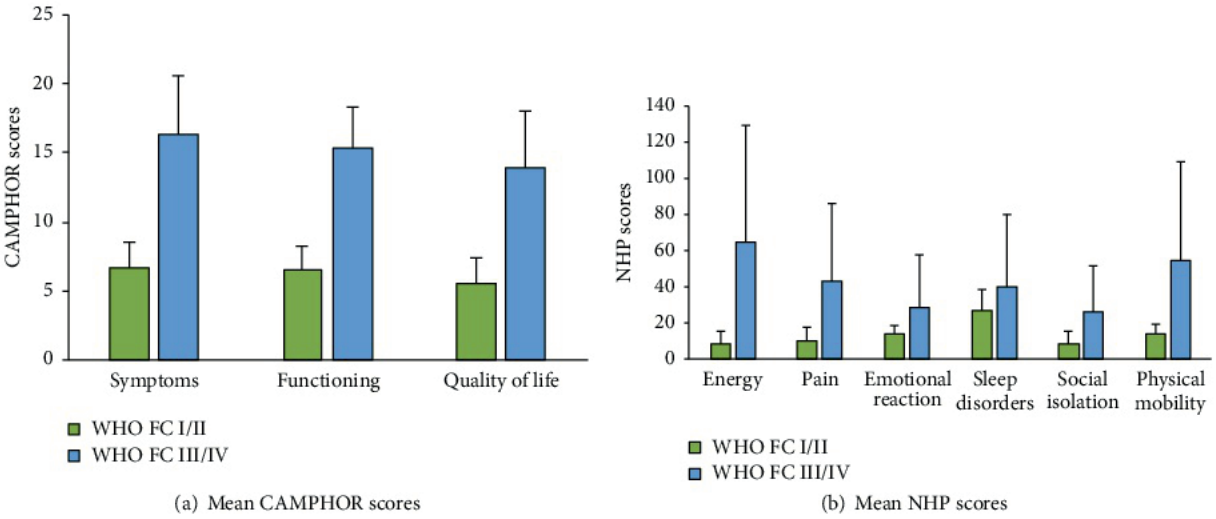
Most patients had PH disease markers compatible with low (28.6%) or intermediate (53.0%) estimated risk of 1-year mortality, according to the 2015 ESC/ERS guidelines risk assessment scale [1]. Most patients were in WHO FC I and II (69.4%). Mean 6MWD was 428 ± 105.8 meters in the overall population, but it was significantly reduced in patients in WHO FC III/IV (320.3 ± 99.4 meters) compared to groups I/II (469.1 ± 75.4 meters; $P < 0.001$).

An arterial oxygen desaturation (94.0 ± 3.4 to 80.5 ± 15.1%) during the 6-MWT was found as well as a moderate elevation of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (668.6 ± 908.4 $\mu$g/mL). Most of patients (87.7%) were under PH-specific therapy, 46.9% in monotherapy and 53.0% in combination therapy. Specific therapy was predominantly administered through oral route (73.5%). A substantial number of patients were under oxygen therapy (40.1.%).

*3.2. Health-Related Quality of Life Assessed through CAMPHOR and NHP.* Overall, the study population showed mean CAMPHOR scores that were indicative of a moderate HRQoL impairment: symptoms (9.6 ± 7.7); functioning (9.3 ± 6.3); quality of life (8.1 ± 7.0). Mean NHP scores were also indicative of a moderate health-related quality of life impairment: energy level (27.0 ± 37.2), pain (20.3 ± 31.1), emotional reactions (18.2 ± 18.6), sleep disturbance (30.2 ± 34.6), social isolation (13.9 ± 24.2), and physical mobility (26.3 ± 26.2). Importantly, mean scores for both CHAMPOR and NHP were significantly worse in patients in WHO FC III/IV, compared to WHO FC I/II (Figure 1). In patients with WHO FC III/IV, all CAMPHOR domains showed significantly higher scores, whereas for NHP the domains showing the worse results were energy level, pain, and physical mobility. In terms of overall QoL, as measured through the QoL domain of CAMPHOR, patients showed comparable patterns, with scores indicative of a moderate impairment of QoL. CAMPHOR and NHP scores according to gender, PH aetiology, oxygen therapy, and PH-specific therapy are explored in Supplementary Materials (available here).

*3.3. Clinical Correlates of Health-Related Quality of Life.* Table 2 explores the relationship between patient demographic and clinical characteristics and CAMPHOR scores. In bivariate analysis, WHO FC, 6MWD, and Borg dyspnoea index were highly correlated with all CAMPHOR domains (correlation >0.5 or <−0.5, with $P < 0.001$); scatterplots for high correlations are shown in Supplementary Materials. Other factors such as age, oxygen use, baseline and maximum heart rate, and oxygen saturation were also significantly correlated with CAMPHOR scores, but with correlations of lower magnitude. In multivariate analysis only 6MWD and Borg dyspnoea index were consistently associated with CAMPHOR scores. Interestingly, for the functioning dimension of CAMPHOR, in multivariate analysis, WHO FC and baseline heart rate were statistically significant factors, whereas Borg dyspnoea index was not a significant factor for this dimension only.

Table 3 explores the relationship between patient demographic and clinical characteristics and NHP scores. The relationships between NHP scores and patient characteristics were highly variable between the different dimensions. In bivariate analysis, WHO FC, 6MWD, and Borg dyspnoea index were highly correlated with the energy level, pain, and physical mobility domains of NHP. However, for the emotional reactions and social isolation domains, Borg dyspnoea index and baseline heart rate were the more relevant factors in terms of bivariate correlation. Also, the sleep disorders dimension only showed significant correlation with gender, Borg dyspnoea index, baseline heart rate, and use of combination therapy, but with correlations of lesser magnitude. In multivariate analysis, WHO FC and 6WMD remained significantly associated with NHP scores in the energy level and physical mobility domains. For the pain domain the significant factors were PH aetiology and maximum heart rate, for the emotional reactions domain the significant factors were Borg dyspnoea index and baseline heart rate, for sleep disorders the significant factor was only gender, and for social isolation the significant factor was only the Borg dyspnoea index. Nonetheless, linear regression models showed lower




(a) Mean CAMPHOR scores

(b) Mean NHP scores

Figure 1: Mean CAMPHOR and NHP scores according to WHO Functional class. CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; NHP: Nottingham Health Profile; WHO FC: World Health Organisation functional class. Error bars represent 95% confidence intervals. Please note that the upper limit for NHP score is 100; confidence intervals are shown here for illustration purposes.

predictive value ($R^2 < 0.3$) for the pain, sleep disorders, and social isolation domains (Table 3). Interestingly, clinically relevant factors such as age, PH aetiology, disease duration, comorbidities, conservative therapy (including oxygen therapy), or PH-specific therapy did not show particularly strong correlations with CAMPHOR or NHP scores, especially in multivariate analyses.

## 4. Discussion

This study characterized the HRQoL of a cohort of Portuguese PH patients with mostly low to intermediate risk of estimated 1-year mortality (low disease severity), using two parallel questionnaires to provide a more comprehensive assessment of overall patient status. HRQoL was moderately impaired for the majority of this PH population. Increased disease severity, assessed by WHO FC, was significantly associated with greater impairment. Patients in WHO FC classes III and IV showed significantly higher scores for all the dimensions of the general and disease-specific instruments, indicative of important HRQoL impairment.

The PH population included in this study had low disease severity (approximately 70% of patients in WHO FC I/II), despite having a mean disease duration over 50 months. This low disease severity can be explained by the fact that most patients were under combination PH-specific therapy at of the time of the study. When compared with other studies that used NHP and CAMPHOR to assess HRQoL in PH, our population had substantially lower disease severity. While most studies included approximately 70% of patients in WHO FC III/IV [28–32], we included 70% of patients on the other end of the spectrum (WHO FC I/II). Such a low profile of disease severity was only previously reported by one study assessing HRQoL through CAMPHOR in a population of patients receiving PH-specific treatment [33]. This patient profile of low disease severity and mortality risk is an important distinctive factor for this study, especially in the current context in which continued treatment innovations will lead to better treatment outcomes in the future. In a context of improved vital and clinical outcomes, improving QoL will be a major treatment goal, thus, studies that evaluate QoL in low disease severity populations can play an important role in establishing better strategies to assess patient outcomes.

CAMPHOR scores in this study were numerically lower than those reported in previous studies [28–31, 33], but in some cases the differences are very small, even below 1 point in the CAMPHOR scores. Lower scores are attributable to low disease severity in this study population. Furthermore, the significantly higher scores showed by patients in WHO FC III/IV were comparable to previous findings [31], which further validates this relationship between CAMPHOR scores and disease severity.

In this study mean NHP scores were particularly high for the dimensions of energy level, sleep disturbance, and physical mobility (ranging from 25–30%). Scores were also elevated for pain and emotional reactions (approximately 20%). Together these findings indicate an overall impairment of HRQoL. A previous study that used the NHP in a PH population with more severe disease (75% in WHO FC III/IV) reported substantially higher scores for all NHP dimensions [32]; NHP scores in our subpopulation of patient in WHO FC III/IV were comparable to the findings of that study, which also supports a relationship between disease severity and NHP scores.

In terms of clinical correlates of HRQoL, the 6MWD and Borg dyspnoea index were the two factors with stronger association with CAMPHOR scores, including scores for the QoL domain. WHO FC was also shown to be a highly relevant factor in bivariate analysis, but since it is intrinsically related to exercise capacity and dyspnoea, in multivariate analysis it only reached statistical significance in the functioning

Table 2: Correlation and multivariate linear regression for the relationship between patient characteristics and CAMPHOR scores.

| Characteristics | Symptoms | | Functioning | | Quality of life | |
|---|---|---|---|---|---|---|
| | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] |
| Age, yrs | 0.240 | | 0.403** | | 0.283* | |
| Work status | | | | | | |
| Full-time | −0.172 | | −0.360* | | −0.166 | |
| Homemaker | 0.095 | | 0.002 | | 0.064 | |
| Retired | 0.090 | | 0.342* | | 0.109 | |
| Etiology | | | | | | |
| PAH/others | 0.328* | | 0.350* | | 0.333* | |
| CTEPH | | | | | | |
| Comorbidities | | | | | | |
| Yes | 0.297* | | 0.228 | | 0.206 | |
| No | | | | | | |
| Functional class | | | | | | |
| I/II | 0.526*** | | 0.627*** | - | 0.505*** | |
| III/IV | | | | 4.74 [1.23; 8.26] | | |
| 6MWD, meters | −0.673*** | −0.03 [−0.05; −0.01] | −0.742*** | −0.02 [−0.04; −0.01] | −0.609*** | −0.03 [−0.04; −0.01] |
| Borg dyspnea | 0.779*** | 1.29 [0.64; 1.93] | 0.652*** | | 0.732*** | 1.19 [0.59; 1.78] |
| HR_bas, bpm | −0.209 | | −0.299* | −0.13 [−0.24; −0.02] | −0.301* | |
| HR_Max, bpm | −0.338* | | −0.411** | | −0.367* | |
| O2Sat_min, mmHg | −0.372** | | −0.335* | | −0.295* | |
| Delta O2Sat | 0.392** | | 0.358* | | 0.333* | |
| Oxygen use | | | | | | |
| Yes | 0.340* | | 0.330* | | 0.324* | |
| No | | | | | | |
| Constant | NA | 19.11 [11.3; 26.9] | | 26.60 [16.9; 36.3] | | 16.71 [9.5; 23.9] |
| $R^2$ adjusted | NA | 0.595 | NA | 0.527 | NA | 0.592 |

For the purpose of brevity only variables with significant results are displayed in the table. The following variables were considered for statistical analysis but did not reach statistical significance: gender, marital status, disease duration, DeltaHR, SBP, DBP, O2Sat_baseline, NT-proBNP, RAP, mPAP, PAOP, CI, PVR, oral anticoagulants, diuretics, calcium channel blockers, PH-specific therapy, PH-specific therapy route; correlation coefficients calculated using Spearman's rank (quantitative versus quantitative variables) or point-biserial (quantitative versus categorical). $R^2$ adjusted represents the proportion of variability explained by the proposed model; 6MWD: 6-minute walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; Borg: Borg dyspnea score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; CI: cardiac index; CTEPH: Chronic thromboembolic pulmonary hypertension; DBP: Diastolic blood pressure; DeltaHR: maximum-baseline heart rate; Delta O2Sat: baseline-minimum oxygen saturation; HR_Bas: baseline heart rate; HR_Max: maximum heart rate; mPAP: mean pulmonary arterial pressure; NA: not applicable; NHP: Nottingham Health Profile; NS: not significant; PAH: pulmonary arterial hypertension; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; O2Sat_min: minimum oxygen saturation; O2Sat_bas: baseline oxygen saturation; SBP: systolic blood pressure; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

domain (where Borg dyspnoea index was not a significant factor). These findings largely agree with previous evidence that found these three measures to be the most relevant predictors of HRQoL in PH [2, 23, 24]. NHP scores showed a more variable relationship with clinical correlates, which was somewhat expected since NHP evaluated various aspects of patients' life in different dimensions. WHO FC and 6MWD remained the more important correlates for the physical functioning dimensions (energy level and physical mobility), but for the remaining dimensions linear regression models had substantially lower predictive value, which could indicate that variables relevant for these dimensions were not considered in this study. We hypothesise that some measures of mental health status could have been important for inclusion in these

Table 3: Correlation and multivariate linear regression for the relationship between patient characteristics and NHP scores.

| Characteristics | NHP | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Energy Level | | Pain | | Emotional reactions | | Sleep disorders | | Social isolation | | Physical mobility | |
| | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] |
| Age, yrs | 0.241 | | 0.233 | | 0.049 | | 0.115 | | 0.128 | | 0.300* | |
| Gender | | | | | | | | | | | | |
| Female | | | | | | | | - | | | | |
| Male | −0.155 | | −0.118 | | −0.216 | | −0.308* | −28.2 [−50.1; −6.3] | −0.241 | | 0.197 | |
| Work status | | | | | | | | | | | | |
| Full-time | −0.226 | | −0.328* | | −0.152 | | −0.239 | | −0.046 | | −0.201 | |
| Homemaker | 0.082 | | 0.009 | | 0.200 | | 0.050 | | 0.112 | | 0.000 | |
| Retired | 0.146 | | 0.303* | | −0.012 | | 0.188 | | −0.044 | | 0.188 | |
| Disease duration, months | −0.134 | | −0.294* | | 0.094 | | −0.179 | | −0.098 | | −0.239 | |
| Etiology | | | | | | | | | | | | |
| PAH/others | | | | - | | | | | | | | |
| CTEPH | 0.344* | | 0.352* | 27.2 [9.4; 45.1] | 0.338* | | 0.242 | | 0.257 | | 0.409** | |
| Comorbidities | | | | | | | | | | | | |
| Yes | 0.295* | | 0.207 | | 0.116 | | 0.098 | | 0.172 | | 0.310* | |
| No | | | | | | | | | | | | |
| Functional class | | | | | | | | | | | | |
| I/II | | - | | | | | | | | | | - |
| III/IV | 0.686*** | 30.7 [11.8; 49.6] | 0.555*** | | 0.309* | | 0.166 | | 0.382** | | 0.649*** | 21.8 [7.60; 36.1] |
| 6MWD, meters | −0.578*** | 5.89 [2.66; 9.13] | −0.507*** | | −0.293* | | −0.189 | | 0.291* | | −0.742*** | −0.12 [−0.18; −0.06] |
| Borg dyspnea | 0.747*** | | 0.544*** | | 0.607*** | 3.79 [2.19; 5.38] | 0.296* | | 0.488*** | 5.03 [2.75; 7.31] | 0.617*** | |
| HR_bas, bpm | −0.117 | | −0.187 | | −0.427*** | −0.42 [−0.78; −0.07] | −0.341* | | −0.406** | | −0.185 | |
| HR_Max, bpm | −0.421*** | | −0.410*** | −0.438 [−0.84; −0.04] | −0.174 | | −0.153 | | −0.214 | | −0.294* | |
| DeltaHR | −0.346* | | −0.298 | | 0.058 | | 0.038 | | 0.024 | | −0.202 | |
| SBP, mmHg | −0.124 | | −0.039 | | −0.144 | | −0.187 | | −0.349* | | −0.041 | |
| O2Sat_min, mmHg | −0.283 | | −0.230 | | −0.285 | | −0.025 | | −0.279 | | −0.353* | |
| Delta O2Sat | 0.323* | | 0.271 | | 0.284 | | 0.032 | | 0.280 | | 0.361* | |
| NT-proBNP, pg/mL | 0.161 | | 0.134 | | 0.063 | | −0.094 | | −0.012 | | 0.318* | |
| Oxygen use | | | | | | | | | | | | |
| Yes | 0.242 | | 0.182 | | 0.204 | | 0.057 | | 0.222 | | 0.328* | |
| No | | | | | | | | | | | | |

Table 3: Continued.

| Characteristics | NHP | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Energy Level | | Pain | | Emotional reactions | | Sleep disorders | | Social isolation | | Physical mobility | |
| | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] | Correlation coefficient | Linear regression coefficient [95% CI] |
| PH specific therapy | | | | | | | | | | | | |
| None | −0.029 | | 0.053 | | 0.057 | | 0.104 | | −0.006 | | 0.058 | |
| Monotherapy | 0.058 | | 0.104 | | 0.012 | | 0.268 | | −0.018 | | −0.011 | |
| Combination therapy | −0.040 | | −0.143 | | −0.051 | | −0.343* | | 0.022 | | −0.028 | |
| Constant | NA | | NA | 58.3 [14.1; 102.4] | NA | 42.3 [13.5; 71.0] | NA | 35.4 [24.7; 46.1] | NA | | n.a. | 71.1 [42.5; 99.8] |
| Adjusted $R^2$ | NA | 0.504 | NA | 0.218 | NA | 0.441 | NA | 0.113 | NA | 0.290 | n.a. | 0.602 |

For the purpose of brevity only variables with significant results are displayed in the table. The following variables were considered for statistical analysis but did not reach statistical significance: marital status, DBP, DeltaBP, Sat_bas, RAP, mPAP, PAOP, CI, PVR, oral anticoagulants, diuretics, calcium channel blockers, PH-specific therapy route; correlation coefficients calculated using Spearman's rank (quantitative versus quantitative variables) or point-biserial (quantitative versus categorical). $R^2$ adjusted represents the proportion of variability explained by the proposed model; 6MWD: 6-minute walk distance test; NT-BNP: N-terminal pro-brain natriuretic peptide; Borg: Borg dyspnea score; CAMPHOR: Cambridge Pulmonary Hypertension Outcome Review; CI: cardiac index; CTEPH: chronic thromboembolic pulmonary hypertension; DBP: diastolic blood pressure; DeltaHR: maximum-basal heart rate; DeltaSat: basal-minimum oxygen saturation; HR_Bas: basal heart rate; HR_Max: maximum heart rate; mPAP: mean pulmonary arterial pressure; NA: not applicable; NHP: Nottingham Health Profile; NS: not significant; PAH: pulmonary arterial hypertension; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; Sat_min: minimum oxygen saturation; Sat_bas: basal oxygen saturation; SBP: Systolic blood pressure; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

models, since other studies have identified conditions such as depression and anxiety to be correlated with HRQoL in PH [21, 22].

This study has limitations inherent to the relatively small sample size and the less severe disease stage of the studied patients. Nonetheless, the study is based on high-quality clinical data, systematically and prospectively collected using a purpose-designed EMR (PAHTool®) at a PH specialised unit, which further ensures data reliability. Additionally, there are also limitations associated with the instruments used to assess HRQoL. Although we used both a general and a disease-specific instrument to provide a more comprehensive picture of overall patient status, other instruments (especially general instruments) could also have been selected. In the future, HRQoL should be evaluated in large Portuguese PH populations (eventually in multicentre studies to attain larger and more diverse samples), employing other highly used general instruments (such as the SF-36 or EQ50) as well as the recently developed disease-specific instruments (emPHasis-10 and PAH-SYMPACT). Characterizing HRQoL with these new instruments in larger and more heterogeneous populations (in terms of severity) will provide an important basis for clinical practice assessments and for comparisons with results from clinical trials. Still, the value of CAMPHOR as the only disease-specific instrument capable of evaluating overall QoL should not be understated. While other recently developed instruments might prove valuable to the clinician, they are only designed to assess HRQoL and, therefore, do not demonstrate actually patient value; this can only be established with an instrument tailored to evaluate QoL, such as the CAMPHOR. This study highlights the importance of CAMPHOR as disease-specific instrument of choice when evaluating HRQoL and QoL in PH patients. It also highlights some aspects of patients' lives that are not fully captured by CAMPHOR (such as mental status) and which should be considered during HRQoL and QoL assessments.

In conclusion, HRQoL is impaired in Portuguese patients with PAH and other forms of pcPH, particularly in patients with increased disease severity. General (NHP) and disease-specific instruments (CAMPHOR) showed comparable HRQoL impairment in this patient population. CAMPHOR also showed a moderate impairment in overall QoL. WHO FC, 6MWD, and Borg dyspnoea index were highly correlated with HRQoL impairment in our cohort, as well as QoL measured through CAMPHOR. In our search for the "best" and "most" practical PROM to evaluate HRQoL and QoL in Portuguese PH patients other highly used general instruments and the newly developed disease-specific instruments will be tested.

## Conflicts of Interest

Abílio Reis is a co-author of the dedicated pulmonary hypertension software PAHTool. The authors have no additional conflicts of interest to disclose.

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## Supplementary Materials

Figure S1: mean CAMPHOR and NHP scores according to gender. Figure S2: mean CAMPHOR and NHP scores according to use of oxygen therapy. Figure S3: mean CAMPHOR and NHP scores according to PH aetiology. Figure S4: mean CAMPHOR and NHP scores according to type of PH-specific therapy. Figure S5: scatterplots for high correlations between CAMPHOR/NHP scores and 6MWD. Figure S6: scatterplots for high correlations between CAMPHOR/NHP scores and Borg dyspnoea. *(Supplementary Materials)*

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## 4.3. Disability and its clinical correlates in Pulmonary Hypertension measured through the World Health Organization Disability Assessment Schedule II (WHODAS 2.0): a prospective, observational study

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ORIGINAL ARTICLE

# Disability and its clinical correlates in pulmonary hypertension measured through the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0): a prospective, observational study

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## ABSTRACT

**Objective:** To characterise the degree of disability in pulmonary hypertension (PH) patients based on the World Health Organisation Disability Assessment Schedule 2.0 (WHODAS 2.0). **Method:** A prospective and observational study of patients with documented PH (N = 46). Patients completed the WHODAS 2.0 questionnaire during a scheduled routine clinical visit, and their demographic and clinical characteristics were retrieved from electronic medical records (EMR). In subsequent visits, selected clinical variables were registered to assess disease progression. **Results:** WHODAS 2.0 scores were indicative of mild to moderate disability for the domains of mobility (22.0 ± 23.2), life activities (23.7 ± 25.5), and participation in society (17.2 ± 15.9), as well as total WHODAS 2.0 score (15.3 ± 15.2). For the domains of cognition (9.1 ± 14.1), self-care (8.3 ± 14.4), and interpersonal relationships (11.7 ± 15.7), scores were lower. Disability scores were, generally, proportional to the PH severity. The main baseline correlates of disability were World Health Organisation (WHO) functional class, fatigue, dyspnoea, 6-minute walking distance (6MWD), and N-terminal pro b-type natriuretic peptide (NT-proBNP). Baseline WHODAS 2.0 scores showed significant associations with disease progression. However, this effect was not transversal to all domains, with only a few domains significantly associated with disease progression variables. **Conclusions:** This PH population shows mild disability, with higher degree of disability in the domains of mobility and life activities. This study is the first one to assess disability in PH using WHODAS 2.0. Further studies should apply this scale to larger PH populations with suitable representations of more severe PH forms.

**Keywords:** Pulmonary hypertension; International Classification of Functioning, Disability and Health; Disability evaluation; HRQOL.

## INTRODUCTION

Pulmonary hypertension (PH) encompasses a set of heterogeneous progressive conditions characterised by increased pulmonary artery pressure, which, if left untreated, leads to right ventricular failure, causing substantial morbidity and, ultimately, premature death.[1] Fortunately, several PH-specific treatments were introduced over the past decades, resulting in considerable gains in terms of long-term patient survival.[2,3] Since then, research shifted towards more intense evaluation of functional capacity and quality of life to ensure effective, patient-centred management of this highly debilitating condition.[4,5] Disability due to PH is multifactorial, depending on factors such as decreased exercise capacity, functional limitation, compensatory physiological mechanisms, psychological impact of the disease, as well as drug adverse effects, and burden of treatment.[6]

Several types of instruments have been used in patients with PH to evaluate functionality, health-related quality of life and quality of life,[4,5] including general assessment questionnaires,[7-9] as well as disease-specific questionnaires.[10-15] Health-related quality of life (HRQOL) has also been evaluated as a prognostic factor and treatment goal in the clinical management of PH.[16] However, to our knowledge, no specific evaluation of functioning and disability in PH populations

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has been done using the standardised functioning and disability classification developed by the World Health Organisation (WHO), the International Classification of Functioning, Disability and Health (ICF).[17]

The ICF does not classify people, but rather interprets their characteristics, namely, body structures and functions, activities and participation, and the influences of the environment, which allows to properly describe functional states. Functioning or disability are considered as a result of a dynamic interaction between health conditions and contextual factors.[17] Using this framework is important, because, although functioning and disability are intercorrelated with HRQOL, this framework provides an objective measure of functioning (*i.e.*, objective ability to perform in a given life domain), while HRQOL assessments provide a subjective measure of well-being (*i.e.*, subjective feeling about the ability to perform in a given life domain).[18] ICF is operationalized through the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0), which is a generic instrument for assessing health status and disability across different cultures and settings.[18,19] WHODAS 2.0 has increasingly been used in clinical practice and described in the medical literature, and it is considered the leading standard measure of disability worldwide.[19] Although being a generic, standardised measure, its psychometric proprieties have been repeatedly validated in diverse populations, locations, and languages, which makes WHODAS 2.0 the tool of choice in comparing disability due to different disease conditions and makes it possible to monitor the impact of health-related interventions.[18,19]

This study aimed to characterise the degree of disability in a population of Portuguese PH patients based on the WHODAS 2.0, and to identify clinical correlates of disability. Additionally, the study purposed to explore the capacity of WHODAS 2.0 in predicting the clinical evolution of PH patients.

## METHODS

### Study design and population

This is a prospective, observational study of prevalent PH patients (confirmed through right heart catheterisation) followed at a single reference centre in the North of Portugal (Pulmonary Vascular Disease Unit of Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal); the centre is part of the European Reference Network for Rare or Low Prevalence Complex Diseases (ERN-LUNG), and covers a region with approximately 3.8 million adult population.

When attending a routine clinical visit, patients were consecutively invited to participate in the study. Patients were eligible to participate if they were ≥ 18 years old and able and willing to give their informed consent. Patients were excluded from the study if they were unable to complete the study data collection forms due to illiteracy or cognitive impairment, or if they were not able to comply with the study protocol, due to other medical conditions or personal circumstances. Patients with group 2 and 3 PH were excluded from the study.

All patients provided their written informed consent prior to enrolment. The study protocol and data collection instruments received favourable opinion by the Ethics Committee of Centro Hospitalar do Porto (Porto, Portugal) and were reviewed and approved by the Portuguese National Data Protection Commission.

### Data collection

Data were collected by self-administering the Portuguese validated version of WHODAS 2.0 questionnaire during a scheduled routine clinical visit. Sociodemographic and disease-specific clinical measures, including haemodynamic ones, were retrieved from the clinical database collected by the dedicated PH software created at the Unit, PAHTool (Inovultus, Santa Maria da Feira, Portugal).

### WHODAS 2.0

WHODAS 2.0 can be self-administered and captures the level of functioning in six domains of life: cognition, mobility, self-care, getting along, life activities (household and work) and participation. The 36-item Portuguese validated version of WHODAS 2.0 was used in this study.[20] WHODAS 2.0 scoring and interpretation were performed according to the WHODAS 2.0 manual.[18] The complex scoring method was used. This scoring consists of three essential steps:

- summing of recoded item scores within each domain;
- summing of all six domain scores;
- converting the summary score into a metric ranging from 0 to 100, in which 0 is no disability and 100 means full disability.

### Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD) or frequency (%). Differences in mean WHODAS scores for different subgroups were tested using one-way ANOVA/Kruskal-Wallis test. For the purposes of analysis, patients with group 1 and group 5 PH were grouped, since there were only three patients in group 5 and all patients received PH-specific treatment.

Bivariate correlation analysis correlating patients' demographic and clinical variables with WHODAS scores was conducted by using Spearman's Rank correlation coefficient (between quantitative variables) and by using point-biserial correlation (between quantitative variables and binary nominal variables). Then, multiple linear regression analysis was established only for the significant correlations to identify possible predictors for WHODAS scores. The method of selecting significant variables was the forward likelihood ratio (stepping method criteria: entry = 0.05; removal = 0.10), and no estimation problems were found. A dummy

variable technique was used to incorporate qualitative independent variables in the regression models.

For the variables measured at the end of the study: disease progression, functional class, 6-minute walking distance (6MWD), N-terminal pro b-type natriuretic peptide (NT-proBNP), and risk classification, prediction models based on WHODAS dimensions or WHODAS total score were established. For the first two variables, binary regression models were used. For the following two variables, linear multiple regression models were derived. For the last variable, an ordinal regression model was conducted (using the probit link function).

Statistical analyses were conducted with Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, United States), and results were considered significant if $p < 0.05$.

## RESULTS

### *Patient characteristics*

Patient characteristics at baseline are summarised in Table 1. This was a prevalent, stable PH population, diagnosed through right heart catheterisation with a mean disease duration of approximately 6.8 years. Most participants were female (63.0%), and the mean age of the study population was 54.5 ± 16.2 years. The most frequent PH aetiologies were chronic thromboembolic pulmonary hypertension (CTEPH) (30.4%), idiopathic/heritable pulmonary arterial hypertension (I/HPAH) (17.4%), connective tissue diseases (CTD) (17.4%), and congenital heart diseases (CHD) (15.2%). For the purpose of analysis, aetiologies are from here on grouped as group 1 and 5 PH (69.6%) and group 4 PH (30.4%). Comorbidities were frequent, present in 67.4% of patients, with a mean of approximately two comorbidities per patient (range = 6; Q1 = 0; Q3 = 3).

Overall, this population showed PH disease markers indicative of low (26.0%), intermediate (54.3%) and high (19.5%) estimated 1-year mortality risk, according to the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines risk assessment scale.[1] Most patients were in WHO functional classes I or II (71.7%), with a mean 6MWD of 415.1 ± 130.1 meters. Self-reported dyspnoea was referred by 54.3% of patients and self-reported fatigue by 39.1%. There was oxygen desaturation (94.0 ± 3.1 to 82.3 ± 9.2) during 6MWT and a 2-fold elevation NT-proBNP levels. PH-specific treatment was used in the vast majority of patients (84.8%), 50% of them in combination therapy, all through oral route (100% of treated patients); only 12.8% were under PH-specific treatment through parenteral route. Adjunctive treatment with oxygen (37.0%), diuretics (50.0%), and oral anticoagulants (60.9%) was frequent.

### *WHODAS 2.0 Disability scores*

WHODAS 2.0 scores were indicative of mild to moderate disability for the domains of mobility (22.0 ± 23.2), life activities (23.7 ± 25.5), and participation in society (17.2 ± 15.9). For the domains of cognition (9.1 ± 14.1), self-care (8.3 ± 14.4), and interpersonal relationships (11.7 ± 15.7), scores were lower. Mean WHODAS 2.0 total score was 15.3 ± 15.2, reflecting the variability between the different domains and indicating only mild general disability in the studied population.

Figure 1 presents mean WHODAS 2.0 scores measured in the study population at baseline according to gender and PH risk group. Mean WHODAS 2.0 scores were generally proportional to the PH risk classification, with higher risk patients showing higher degrees of disability. Mean WHODAS 2.0 total score was 8.7 ± 9.0 for low-risk patients, 15.4 ± 14.9 for intermediate-risk patients, and 24.1 ± 19.2 for high-risk patient ($p = 0.150$). As for the different domains, higher risk patients generally showed numerically higher WHODAS 2.0 scores, but the differences only reached statistical significance for the interpersonal relationship domain ($p = 0.021$). Women did not show significantly different scores from men for any domain.

### *Clinical correlates of disability*

In bivariate analysis (Table 2), WHO Functional class and Borg fatigue index were the variables that showed stronger correlations with all domains, as well as the total WHODAS 2.0 score (correlation generally > 0.5 or < -0.5). For the life activities domain, fatigue was also strongly correlated (0.512), whereas for the participation in society domain the Borg dyspnea index was also strongly correlated (0.571). The total WHODAS 2.0 score was, in addition, strongly correlated with years of schooling (-0.501), fatigue (0.515), and the Borg dyspnea index (0.561). Figures S1 e S2 (Appendix) show scatterplots for correlations between WHODAS 2.0 scores and 6MWD. The Appendix is available online at http://jornaldepneumologia.com.br/link

Multivariate analysis (Table 3) showed substantially different results for each WHODAS 2.0 domain. For the cognition domain, the significant variables were WHO functional class and pulse pressure (systolic minus diastolic blood pressure). For the mobility domain, the significant variables were WHO functional class and self-reported fatigue. For the self-care domain, only WHO functional class was a statistically significant variable. For the interpersonal relationship domain, the Borg fatigue index and NT-proBNP were the significant variables. For the life activities domain, self-reported fatigue was the significant variable. For the domain of participation in society, the years of schooling, the Borg fatigue index, and pulse pressure were significant variables. Overall, for the total WHODAS 2.0 score, only self-reported fatigue and WHO functional class were significant factors in multivariate analysis.

### *Disease progression*

Table 4 presents the evolution of the main PH disease markers at the final study visit. Over a mean follow-up time of approximately 11 months, few

**Table 1.** Sociodemographic and clinical characteristics of the study population at baseline.

| Characteristics | PH patients (N = 46) |
|---|---|
| Female, n (%) | 29 (63.0) |
| Age, years | 54.5 ± 16.2 |
| Marital status, n (%) | |
| Single/divorced/widowed | 14 (30.4) |
| Married/cohabitation | 32 (69.6) |
| Working status, n (%) | |
| Full-time | 10 (21.7) |
| Retired/homemaker | 25 (54.3) |
| Unemployed | 11 (23.9) |
| Schooling, n (%) | |
| No formal education | 6 (13.0) |
| Basic education (up to 9 years) | 30 (65.2) |
| Secondary education (12 years) | 6 (13.0) |
| University education | 4 (8.7) |
| Disease duration, days | 2,487.2 ± 3,199.9 |
| PH aetiology, n (%) | |
| PAH | 29 (63.0) |
| I/HPAH | 8 (17.4) |
| CTD | 8 (17.4) |
| CHD | 7 (15.2) |
| PoPH | 4 (8.7) |
| HIV | 2 (4.3) |
| Other | 3 (6.5) |
| Splenectomy | 2 (4.3) |
| Sarcoidosis | 1 (2.2) |
| CTEPH | 14 (30.4) |
| Comorbidities, n (%) | 31 (67.4) |
| Comorbidities number per patient | 1.9 ± 1.8 |
| Self-reported dyspnoea, n (%) | 25 (54.3) |
| Self-reported fatigue, n (%) | 18 (39.1) |
| WHO Functional class, n (%) | |
| I/II | 33 (71.7) |
| III/IV | 13 (28.3) |
| NT-proBNP, pg/mL | 401.1 ± 477.9 |
| 6MWD, meters | 415.1 ± 130.1 |
| Borg (dyspnoea) | 1.7 ± 2.6 |
| Borg (fatigue) | 2.8 ± 2.8 |
| $O_2$Sat_bas, % | 94.0 ± 3.1 |
| $O_2$Sat_mn, % | 82.3 ± 9.2 |
| Delta $O_2$Sat | 11.9 ± 7.8 |
| SBP, mmHg | 117.2 ± 20.2 |
| DBP, mmHg | 67.1 ± 13.2 |
| Pulse pressure, mmHg | 50.1 ± 13.9 |
| Creatinine, mg/dL | 0.9 ± 0.3 |
| RAP, mmHg | 7.9 ± 4.4 |
| mPAP, mmHg | 46.0 ± 15.9 |
| CI, L/min/m$^2$ | 3.3 ± 1.1 |
| PVR, Wood units | 6.0 ± 3.4 |
| PH risk classification, n (%) | |
| Low | 12 (26.0) |
| Intermediate | 25 (54.3) |
| High | 9 (19.5) |
| Oxygen therapy, n (%) | 17 (37.0) |
| Oral anticoagulants, n (%) | 28 (60.9) |
| Diuretics, n (%) | 23 (50.0) |
| PH-specific therapy, n (%) | 39 (84.8) |
| Number of PH-specific drugs | 1.5 ± 0.9 |
| Oral route, n (%) | 39 (84.8) |
| Parenteral route, n (%) | 5 (10.9) |
| Other drugs, number | 2.2 ± 2.2 |

Data displayed as mean ± standard deviation (SD), except when otherwise indicated. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; I/HPAH: idiopathic/heritable pulmonary arterial hypertension; CTD: connective tissue diseases; CHD: congenital heart diseases; PoPH: portopulmonary hypertension; HIV: human immunodeficiency virus; CTEPH: chronic thromboembolic pulmonary hypertension; WHO: World Health Organization; NT-proBNP: N-terminal Pro b-type natriuretic peptide; 6MWD: 6-minute walking distance; SBP: systolic blood pressure; DBP: diastolic blood pressure; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; O2Sat_mn: minimum oxygen saturation; Sat_bas: baseline oxygen saturation.

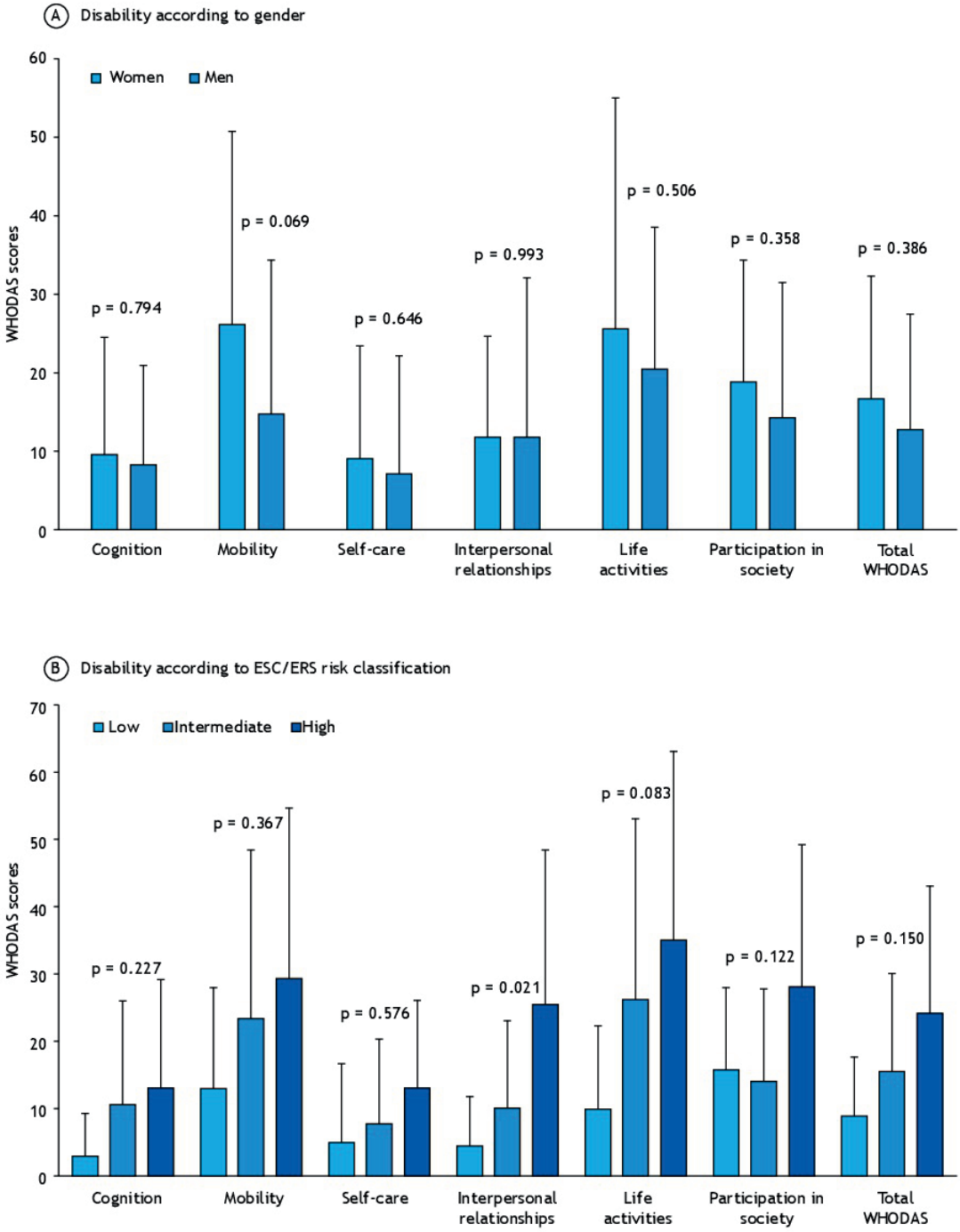


**Figure 1.** Mean World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores in the study population at baseline according to (A) gender and (B) pulmonary hypertension risk classification. Error bars represent standard deviations.

patients (13.0%) showed disease progression. There was a slight improvement in WHO functional class, with the proportion of patients in functional classes I/II increasing from 71.7 to 76.1%. 6MWD also increased slightly from baseline to final visit (mean improvement of 5.6 ± 85.8 meters). Mean levels of NT-proBNP increased substantially from baseline to final visit, from a 2-fold elevation at baseline to a 3-fold elevation at final visit. The number of patients in intermediate and high risk slightly increased from 54.3 to 60.9% and from 19.5 to 23.9%, respectively.

Table 5 explores the association between baseline WHODAS 2.0 scores and patient evolution in terms of 6MWD and NT-proBNP levels at final visit. In bivariate analysis, 6MWD at final visit was strongly associated with all WHODAS 2.0 dimensions except cognition, whereas

**Table 2.** Correlation results for the relationship between patient characteristics at baseline and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores.

| | Cognition | Mobility | Self-care | Interpersonal relationship | Life activities | Participation in society | Total |
|---|---|---|---|---|---|---|---|
| Age, years | 0.042 | 0.306* | 0.182 | 0.371* | 0.340* | 0.148 | 0.405** |
| Schooling, years | -0.217 | -0.400** | -0.308* | -0.458** | -0.452** | -0.411** | -0.501*** |
| Working status | 0.066 | 0.213 | 0.227 | 0.232 | 0.232 | 0.106 | 0.317* |
| PH aetiology | 0.191 | 0.175 | 0.105 | 0.328* | 0.295* | 0.209 | 0.343* |
| Self-reported dyspnoea | 0.207 | 0.146 | 0.175 | 0.341 | 0.337* | 0.190 | 0.273 |
| Self-reported fatigue | 0.451** | 0.540** | 0.369* | 0.222 | 0.512*** | 0.390** | 0.515*** |
| No | | | | | | | |
| Yes | | | | | | | |
| WHO Functional class | 0.629*** | 0.591*** | 0.590*** | 0.598*** | 0.560*** | 0.596*** | 0.671*** |
| I/II | | | | | | | |
| III/IV | | | | | | | |
| 6MWD, meters | -0.389 | -0.417** | -0.229 | -0.349* | -0.393** | -0.212 | -0.419** |
| Borg (dyspnoea) | 0.293 | 0.467** | 0.251 | 0.476** | 0.424** | 0.571*** | 0.561*** |
| Borg (fatigue) | 0.583*** | 0.627*** | 0.420** | 0.598*** | 0.554*** | 0.699*** | 0.738*** |
| Pulse pressure | -0.401** | -0.207 | -0.400** | -0.260 | -0.217 | -0.298* | -0.233 |
| Sat_bas, mmHg | -0.074 | -0.044 | -0.175 | -0.206 | -0.326* | -0.035 | -0.338 |
| Creatinine (mg/dL) | 0.200 | 0.052 | 0.029 | 0.210 | 0.340* | 0.146 | 0.243 |
| NT-proBNP, pg/mL | 0.231 | 0.111 | 0.193 | 0.405** | 0.148 | 0.192 | 0.272 |
| CI, L/min/m$^2$ | -0.198 | 0.068 | -0.044 | -0.394* | -0.257 | -0.074 | -0.167 |
| PVR, Wood units | 0.091 | -0.140 | 0.025 | 0.159 | 0.169 | 0.134 | 0.025 |
| Oxygen Therapy | 0.191 | 0.306* | 0.290* | 0.336* | 0.295* | 0.227 | 0.309* |
| Risk classification[a] | 0.220 | 0.211 | 0.154 | 0.399** | 0.327* | 0.144 | 0.283 |
| Low | | | | | | | |
| Intermediate | | | | | | | |
| High | | | | | | | |

PH: pulmonary hypertension; WHO: World Health Organization; 6MWD: 6-minute walk distance test; Sat_bas: basal oxygen saturation; NT-proBNP: N-terminal pro b-type natriuretic peptide; CI: cardiac index; PVR: pulmonary vascular resistance. For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: gender, marital status, disease duration, comorbidities, number of comorbidities, body mass index (BMI), basal heart rate (HR_Bas), maximum heart rate (HR_Max), maximum - basal heart rate (DeltaHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), minimum oxygen saturation (Sat_min), basal - minimum oxygen saturation (DeltaSat), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), haemoglobin, haematocrit, oral anticoagulants, diuretics, PH specific therapy, number of PH specific drugs, PH specific oral route, PH specific parenteral route, other drugs, number of other drugs. Correlation coefficients calculated using Spearman's rank (quantitative *vs.* quantitative variables) or point-biserial (quantitative *vs.* categorical). [a]Estimated risk of 1-year mortality, according to the 2015 ESC/ERS guidelines risk assessment scale. *p < 0.05; **p < 0.01; ***p < 0.001. Correlations with p < 0.01 are presented in bold.

NT-proBNP levels only showed a weak association with the cognition, mobility, and life activities domains. In multivariate analysis, 6MWD at final visit was significantly associated with the interpersonal relationships domains, whereas NT-proBNP was significantly associated with the mobility and self-care domains.

The relationship between WHODAS 2.0 scores and WHO functional class and occurrence of disease progression was assessed through binary logistic regression, with no significant results for any of WHODAS domains. Nonetheless, total WHODAS 2.0 score at baseline was significantly associated with WHO functional class at final visit (*odds ratio*—OR: 1.124 [1.051–1.203; p < 0.001]).

Lastly, the predictive power of WHODAS 2.0 scores in terms of risk classification at last visit was assessed through ordinal regression. This analysis revealed a statistically significantly association only for the mobility domain (estimate: 3.919 [0.746–7.092]; p < 0.05). The correct overall classification percentage between the observed and the predicted categories was 66.7%, with the following distribution of risk: low (14.2%), intermediate (89.3%), and high (54.5%).

## DISCUSSION

This study provides, to our knowledge, the first characterisation of disability in patients with PH based on the WHODAS 2.0 standardised assessment instrument. Using this type of tool to access disability across varied populations—both in terms of location and diseases states—, it can provide valuable insights in establishing better clinical care and improving overall public health. WHODAS 2.0 is particularly useful for these types of assessments, because it is based on the biopsychological

**Table 3.** Multivariate linear regression (β coefficients and the correspondent 95%CI) for the relationship between patient characteristics at baseline and World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores.

| | Cognition | Mobility | Self-care | Interpersonal relationship | Life activities | Participation in society | Total |
|---|---|---|---|---|---|---|---|
| Schooling, years | | | | | | -5.4 [-10.4;-0.3] | |
| Self-reported fatigue | | - | | | - | | - |
| No | | 18.7 | | | 36.3 | | 9.2 |
| Yes | | [8.3;29.0] | | | [20.8;51.8] | | [2.7;15.8] |
| WHO Functional class | - | - | - | | | | - |
| I/II | 19.7 | 24.5 | 15.3 | | | | 18.1 |
| III/IV | [12.8;26.7] | [13.2;35.9] | [8.2;22.3] | | | | [10.9;25.2] |
| Borg (fatigue) | | | | 2.7 [1.6;3.8] | | 2.58 [1.23;3.94] | |
| Pulse pressure | -0.23 [-0.45;-0.01] | | | | | -0.37 [-0.63;-0.11] | |
| Creatinine (mg/dL) | | | | | 34.3 [12.5;56.1] | | |
| NT-proBNP, pg/mL | | | | 0.01 [0.00;0.01] | | | |
| Constant | 15.1 [3.5;26.8] | 7.2 [1.3;13.1] | | | | 34.2 [16.7;51.8] | |
| $R^2$ Ajustated | 0.477 | 0.534 | 0.301 | 0.445 | 0.483 | 0.454 | 0.539 |

CI: cardiac index; WHO: World Health Organisation; NT-proBNP: N-terminal pro b-type natriuretic peptide. For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: age, gender, marital status, working status, pulmonary hypertension (PH) aetiology, disease duration, self-reported dyspnoea, comorbidities, number of comorbidities, body mass index (BMI), 6-minute walk distance test (6MWD), Borg (dyspnoea), basal heart rate (HR_Bas), maximum heart rate (HR_Max), maximum - Basal heart rate (DeltaHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), minimum oxygen saturation (Sat_min), basal oxygen saturation (Sat_bas), basal - minimum oxygen saturation (DeltaSat), right atrial pressure (RAP), mean pulmonary arterial pressure (mPAP), haemoglobin, haematocrit, CI, pulmonary vascular resistance (PVR), oxygen therapy, oral anticoagulants, duretics, PH specific therapy, number of PH specific drugs, PH specific oral route, PH specific parenteral route, other drugs, number of other drugs, ESC/ERC risk classification. $R^2$ Adjusted represents the proportion of variability explained by the proposed model. Relationships with $p < 0.01$ are presented in bold.

model of functioning and disability defined by the ICF, which takes into account the degree on disability actually perceived by the individuals and, therefore, constitutes a better basis for targeted therapeutic interventions and public health policies. Also, being a standardized tool, it allows comparative studies with other health conditions and in different contexts.

The population of PH patients in this study showed low to intermediate PH disease severity, despite a disease duration of approximately seven years. Low to intermediate disease severity is reflected in the degree of disability observed in the study population according to WHODAS 2.0 scores, which showed mostly mild disability for individual WHODAS 2.0 domains and WHODAS 2.0 total score (15.3 ± 15.2). The domains of mobility and life activities were the ones in which patients showed more disability, which could be expected given the impairments in exercise capacity that characterise PH.[1]

The degree of disability observed in this population is markedly lower than previous reports in populations with cardiorespiratory conditions with somewhat comparable disease manifestations.[19] Racca et al. assessed disability in a population of ischaemic heart disease patients, reaching a mean total WHODAS 2.0 score of approximately 24 points (with a score of approximately 50 for the life activities domain).[21] Pedro-Cuesta et al. assessed disability in a population of patients with chronic obstructive pulmonary disease, chronic heart failure, or stroke and found total WHODAS 2.0 scores of 26, 38, and 28, respectively.[22] In a large population of patients with chronic diseases—including patients with ischemic heart disease—, Garin et al. reported a total WHODAS 2.0 score of 24.8 ± 19.3, with scores in the life activities domain of 37.[23] The authors provided, however, estimates of disability according to disease severity, and our results are, actually, comparable to those of patients with ischaemic heart disease of mild to moderate severity.[23]

These findings support the assertion that the low degree of disability observed in our study population can be explained by the disease severity endured by the patients. We hypothesise that the relatively mild disability in the context of this highly debilitating and progressive disease is associated with the type of clinical management provided to these patients, which are followed in a highly-specialised PH treatment unit, without difficulties in accessing approved PH-specific drugs. Importantly, 84.8% of patients were under treatment with PH-specific drugs, 59% in combination therapy, which is expected to result in better disease

control and substantially fewer disease manifestations, thus vastly improving overall patient functioning.

The main baseline variables associated with disability measured through WHODAS 2.0 in this study cohort were WHO functional class, fatigue (and Borg fatigue index), dyspnoea (and Borg dyspnoea index), 6MWD, and NT-proBNP. These results are largely in agreement with previous studies assessing general health status and health-related quality of life in PH populations.[5] Several studies identified WHO functional class,[24-28] fatigue,[24,25] and dyspnoea[24,25] to be highly associated with overall health status and health-related quality of life. Additionally, there was an important negative correlation between education and scores for the domain of participation in society; this effect is, however, likely associated with the social involvement of participants in their communities, irrespective of PH.

**Table 4.** Clinical characteristics of the study population at final visit (end of study).

| Characteristics | PH patients (n = 46) |
|---|---|
| Follow-up time, days | 337.4 ± 140.1 |
| Disease progression, n (%) | |
| Yes | 6 (13.0) |
| No | 40 (87.0) |
| WHO Functional class, n (%) | |
| I/II | 35 (76.1) |
| III/IV | 11 (23.9) |
| 6MWD, meters | 412.7 ±134.8 |
| NT-proBNP, pg/mL | 585.6 ± 1046.3 |
| Risk classification, n (%) | |
| Low | 7 (15.2) |
| Intermediate | 28 (60.9) |
| High | 11 (23.9) |

PH: Pulmonary hypertension; WHO: World Health Organisation; 6MWD: 6-minute walking distance; NT-proBNP: N-terminal pro b-type natriuretic peptide. Data displayed as mean ± standard deviation (SD), except when otherwise indicated.

Several variables that are usually important for the clinical management of PH patients showed only weak or even no correlation with disability scores. Age and PH aetiology did not reach statistical significance in the multivariate regression model, which indicates that other variables are more important in a multivariate context. Similarly, PH risk classification showed sporadic significant correlations with disability scores in bivariate analysis, but it was not considered a significant factor in the multivariate model. On the other hand, disease duration, PH-specific treatment, and the presence of comorbidities did not even show significant correlations in bivariate analysis. These results could potentially be explained by reduced variability in this relatively small population.

When using WHODAS 2.0 scores at baseline to predict evolution of PH markers over the 11-month period of the study, disability scores were only robustly predictive of 6MWD and WHO functional class evolution. There were a strong negative correlation between the mobility domain and 6MWD at final visit and a strong positive correlation between WHODAS 2.0 total score and WHO functional class at last visit, as would also be expected in both cases.

Some limitations of this study should be considered. The study had a moderate sample size (N = 46) even in the context of PH, which is an infrequent

**Table 5.** Correlation and multivariate linear regression for the relationship between World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores and patient evolution measured at final visit (end of study).

| | 6MWD | | NT-proBNP | |
|---|---|---|---|---|
| WHODAS 2.0 Dimensions | Correlation coefficient | Linear regression β [95%CI] | Correlation coefficient | Linear regression β [95%CI] |
| Cognition | -0.299 | 1.82 [-1.05;4.70] | 0.351* | 20.80 [3.51;45.11] |
| Mobility | -0.616*** | -3.48** [-5.95;-1.01] | 0.361* | 36.88*** [16.42;57.34] |
| Self-care | -0.527*** | 0.420 [-3.11;3.95] | -0.075 | -65.75*** [-93.22;-38.29] |
| Interpersonal relationship | -0.599*** | -5.19*** [-7.97;-2.40] | 0.207 | 14.32 [-8.46;37.11] |
| Life activities | -0.508*** | -0.909 [-2.86;1.04] | 0.300* | -4.79 [-21.28;11.70] |
| Participation in society | -0.450*** | 3.13 [-0.42;6.67] | 0.267 | 2.35 [-27.69;32.39] |
| Constant | NA | 494.5*** [449.7;539.2] | NA | 38.0 [-338.3;414.3] |
| $R^2$ Ajustated | NA | 0.498 | NA | 0.401 |

6MWD: 6-minute walk distance test; NT-proBNP: N-terminal pro b-type natriuretic peptide: NA: not applicable; 95%CI: confidence interval of 95%. For the purpose of brevity, only variables with significant results are displayed in the table. The following variables were considered for statistical analysis, but did not reach statistical significance: Delta_6MWD; Delta NT-proBNP. Correlation coefficients calculated using Spearman's rank (quantitative *vs.* quantitative variables) or point-biserial (quantitative *vs.* categorical). $R^2$ Adjusted represents the proportion of variability explained by the proposed model. *p < 0.05; **p < 0.01; ***p < 0.001.

condition. The sample was compounded with only a small number of patients with severe forms of PH (19.5%) that are expected to show substantially higher degrees of disability, which limits comparisons with previous reports from populations with higher levels of disability. Further studies should focus on assessing more heterogeneous PH populations in terms of disease severity. Additionally, the study had a relatively short mean follow-up time, which could hinder the assessment of the predictive value of baseline WHODAS 2.0 scores, since few events of interest occurred throughout the period of the study.

In conclusion, this population of Portuguese PH patients shows mild disability as assessed through WHODAS 2.0, which can be associated with low to intermediate disease severity. Higher degree of disability is found in the domains of mobility and life activities. The main clinical correlates of disability in this population are WHO functional class, fatigue, and dyspnoea. WHODAS 2.0 scores at baseline predict 6MWD and WHO functional class over an 11-month follow-up period.

This study was the first one to assess disability in PH using WHODAS 2.0. Further studies should apply this scale to larger PH populations with suitable representations of more severe forms of PH.

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APPENDIX

# Disability and its clinical correlates in pulmonary hypertension measured through the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0): a prospective, observational study

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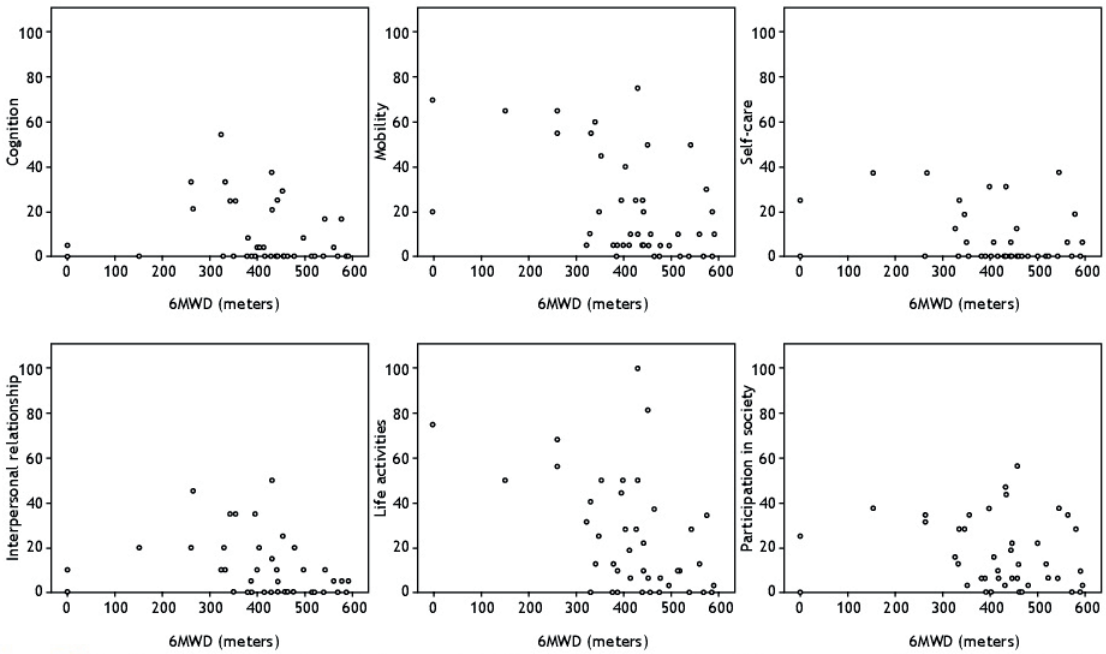


**Figure S1.** Scatterplots for correlations between World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores and 6-minute walk distance test (6MWD).

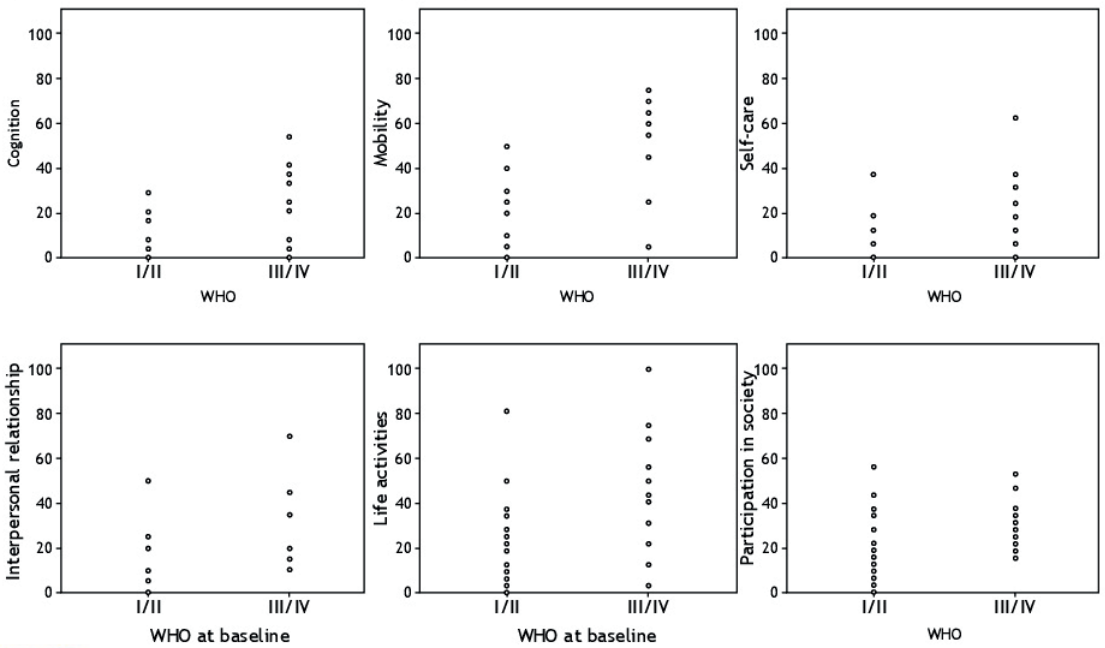


**Figure S2.** Scatterplots for correlations between World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) scores and World Health Organization (WHO) Functional Class.

# 5. CHAPTER V – What has been achieved, prospects for future developments, and conclusions

## 5.1. Integrated discussion, clinical implications and prospects for future developments

A national healthcare organization system for PH, in line with that of most European countries and according to European Commission recommendations for rare diseases, is being implemented in Portugal. Four referral centers for PH were designated by the national authorities, in 2013. One of these centers integrates the European Reference Network for rare and complex low prevalence diseases. These centers built regional reference networks for PH, covering all the country. A dedicated reimbursement budget for referral centers was approved and helped to break barriers for the acceptance of these highly costly patients by healthcare providers.

However, some organizational gaps remain: there is not yet a regular program of pulmonary endarterectomy for CTEPH patients, neither a lung transplantation program for PAH patients not responding to medical therapy, and, most importantly, there is not yet a true commitment of health authorities to improve and regulate the organization achieved, namely implementing the obligation to register all patients by the official referral centers to provide data for planning (epidemiology) and regulation (good practices and costs).

Although cross-border healthcare provided by some European reference centers helps to resolve part of the PH surgical treatment gap, most of the patients with indication for these types of surgery do not accept the risk of doing it abroad. It is time to improve access of these patients to these successful and cost-saving surgeries, nominating and supporting the training of one national center in those procedures. These political options are being discussed with national authorities, with the active involvement of the Portuguese PH patient's association.

Development and validation, by the national and international PH community, of a dedicated information system for PH (PAHTool™) was achieved. Continuous development of the system and customization for the users is now an obligation of its authors. Its integration in general EHR generating systems is a priority to make it ever easier to use in the daily practice of PH teams. Its continuous adaptation for real-world registries, clinical trials and other types of research is compelling and is under continuous development. Incorporation of patient-reported data (QoL/Disability questionnaires and data from wearable technologies) and connection with other databases (e.g. biobanks, biomarkers, and others) will help move towards precision/personalized medicine and will follow the recommendations to integrate patients' perspectives in the early stages of drug development according with the FDA's Patient-Focused Drug Development (PFDD) initiative.

Future implementation of an international registry, involving all centers using PAHTool™, with a common eCRF and precise objectives will surely help to know better PH epidemiology, patient phenotypes and outcomes.

The expected connection of PAHTool™ with the ERN warehouse of registries, currently in progress, will facilitate PH ERN centers data exports and will enrich this large database that is currently being built.

From a national registry and two cohort studies that assessed patient characteristics and clinical outcomes in Portuguese PH patients, several relevant findings emerged. Although PAH is historically associated with younger patients, there is a clear trend for aging populations in I/HPAH and CTD-PAH sub-groups. The classical female predominance continues to be seen in these studies.

In the Portuguese population, CHD-associated PAH is highly prevalent, compared to what would be expected from international settings. On the other hand, PAH associated with drugs, toxins, HIV, and portal hypertension are less frequent than what would be expected. These findings are an alert to the need of improving early surgical repair of congenital heart diseases and the awareness for these missing etiologies. These issues are part of the Portuguese PH scientific community concerns and integrate their permanent campaigns about PH.

Markers of disease progression tended to improve overtime with the introduction of innovative treatments. Survival improved over time mainly for patients with non-I/HPAH etiologies. The availability of all PAH-specific drugs leads to improvements in patient outcomes, although prostanoids remain underused in etiologies beyond I/HPAH. Surgical treatments for PH are also underused in Portugal due to the lack of expertise in the national centers.

Establishing pre-defined diagnosis/treatment/follow-up protocols is crucial to achieve better and more personalized patient care that leads to improved clinical outcomes and survival. Well-designed EHR with appropriate eCRFs can play an important role in providing data for epidemiological purposes, as well as to assess patient outcomes, which can ultimately be very useful in supporting the development of better policies.

The current Portuguese organizational model, while requiring further improvement, had a significant impact in improving outcomes of PH patients. Therefore, this strategy should be maintained, with continued assessment of outcomes. Some improvements to the current model can be outlined, namely extending the use of early and aggressive treatment strategies to non-I/HPAH etiologies and increasing the access to PH surgical treatments (PEA and lung transplantation).

Traditionally, HRQoL/QoL evaluation in PH was limited to clinical trials and was typically considered as a secondary endpoint. However, progressively, these assessments have been included in the routine evaluation of PH patients and in the future these patient-focused measures will probably be considered markers of disease severity comparable to the typically used clinical markers.

We have witnessed substantial developments in the HRQoL/QoL questionnaires used in PH, with a move from general instruments (e.g. SF36, NHP, and others) towards specific instruments (CAMPHOR), and most recently to patient-centered specific-PH PROMs (PAH-SYMPACT and emPHasis-10). These PH PROMs were developed in line with the FDA's PFDD initiative and EMA's guidelines, which aim to include the patients' perspective in the early stages of product/drug development and are also being used in routine clinical practice since they are easy to apply, time-saving compared to existent questionnaires, and they serve the patient-centered/patient-engaged/self-managed medicine perspective.

We validated a specific-PH questionnaire (CAMPHOR) for the pre-capillary PH Portuguese-speaking population, and we compared it with a general instrument (NHP) showing that they had similar capacity to evaluate HRQoL. However, only CAMPHOR

was able to evaluate QoL, once it is the only one designed to specifically assess overall QoL in the PH population. However, it also has some limitations: it is difficult to apply (long, time-consuming, needs external interpretation) and it is not ideal to assess mental/emotional status. PAH-SYMPACT and emPHasys-10 can be valuable tools to assess PH patients given their patient-centered design and, thus, validation of both instruments for the Portuguese speaking population is already in course.

The assessment of disability has not, historically, been subject of much study in the PH population. However, with the trend towards patient-centered/patient-engaged/self-managed medicine this issue is becoming increasingly relevant. Additionally, disability evaluation is important for legal assessment of work ability and approval for government-sponsored Social Security or employer-sponsored medical disability benefits. Experience shows that most patients with PH experience difficulty in qualifying for medical disability status, specially the PAH patient, typically a young patient with relatively normal physical examination. Legal definitions of disability for PH patients are scarce, based on criteria for cardiopulmonary diseases and most of the times of subjective interpretation. So, it is of major importance to have specific and objective measures that can be used in this group of patients. The ICF schedule and, specifically, WHODAS can facilitate the uniformization of criteria to define the degree of disability in a more objective manner. We assessed the degree of disability in a Portuguese population using WHODAS 2.0 and found that disability is really associated with disease severity as established by other clinical markers. These findings suggest that WHODAS 2.0 could be a valuable tool to objectively establish the degree of patient disability in PH. More studies with larger Portuguese PH population samples are needed and are being planned.

## 5.2. Conclusions

For the first time, a nationwide registry was implemented in Portugal providing data for better understanding of the characteristics of the Portuguese PH population and for healthcare planning. A delayed diagnosis and absence of some etiologies were the most remarkable differences when compared with other national registries. A greater commitment of the PH clinical community and national authorities is needed to improve PH public awareness and early referral to the officially designated referral PH centers.

Two real-world data publications from a Portuguese expert referral center showed patient characteristics and outcomes, including survival, similar to other referral centers or international registries.

Patient-centered health outcomes are especially important for the management of diseases that have a marked negative impact in quality of life, as it is the case of PH. A PH-specific QoL questionnaire (CAMPHOR) was translated and successfully validated for use in the European Portuguese-speaking population and is now available for use in clinical routine and research activities.

Health-related QoL may be significantly impaired in patients with PH. Both CAMPHOR, a PH-specific questionnaire, and NHP, a general questionnaire, showed to

adequately assess HRQoL. However, only CAMPHOR showed to capture QoL impairment.

WHO ICF and WHODAS 2.0 questionnaire are valuable tools for the assessment of patients' disability. We tested WHODAS 2.0 questionnaire for the first time in a PH population and it showed that the degree of disability is well correlated with disease severity. Further studies should be conducted to fully characterize the clinical value of ICF and WHODAS in PH, which is a highly disabling disease.

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